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(71) Applicant(s)
Merck & Co Inc

(Incorporated in USA - New Jersey)

P O Box 2000, 126 East Lincoln Avenue, Rahway, New Jersey 07065-0900, United States of America

(72) Inventor(s)
Roy G Smith
Glenn J Gormley
William J Polvino

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(74) Agent and/or Address for Service
I J Hiscock
Merck & Co. Inc, European Patent Department, Terlings Park, Eastwick Road, HARLOW, Essex, CM20 2QR, United Kingdom

(54) **Treatment of congestive heart failure with a growth hormone secretagogue**

(57) A growth hormone secretagogue is useful, alone or in combination with an antihypertensive agent, for the prevention or the treatment of congestive heart failure.

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TITLE OF THE INVENTION

TREATMENT OF CONGESTIVE HEART FAILURE WITH A GROWTH HORMONE SECRETAGOGUE

BACKGROUND OF THE INVENTION

Congestive heart failure (CHF; cardiac failure) is a condition in which weakened heart function exists together with a build-up of body fluid. Cardiac failure occurs when cardiac output is insufficient to meet metabolic demands of the body, or when the heart cannot meet the demands of operating at increased levels of filling/diastolic pressure.

Congestive heart failure may be caused by many forms of heart disease. Common causes of congestive heart failure include: narrowing of the arteries supplying blood to the heart muscle (coronary heart disease); prior heart attack (myocardial infarction) resulting in scar tissue large enough to interfere with normal function of the heart; high blood pressure; heart valve disease due to past rheumatic fever or an abnormality present since birth; primary disease of the heart muscle itself (cardiomyopathy); defects in the heart present at birth (congenital heart disease); and infection of the heart valves and/or heart muscle itself (endocarditis and/or myocarditis). Each of these disease processes can lead to congestive heart failure by reducing the strength of the heart muscle contraction, by limiting the ability of the heart's pumping chambers to fill with blood due to mechanical problems or impaired diastolic relaxation, or by filling the heart's chambers with too much blood.

Numerous compounds are known in the art to be useful for the prevention and treatment of congestive heart failure, including e.g., α-adrenergic antagonists, angiotensin II antagonists, angiotensin-converting enzyme inhibitors, β-adrenergic antagonists, antihypertensives, calcium channel blockers, diuretics, potassium channel opening vasodilators, renin inhibitors, and serotonin antagonists.

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects

on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. The cardiac effects of growth hormone have been reviewed, and it is suggested that growth hormone plays a role in the modulation of cardiac performance and the maintenance of normal cardiac structure and performance. L. Sacca, et al., Endocrine Rev., 15(5) 555-573 (Oct. 1994).

A deficiency in growth hormone secretion can result in various medical disorders, depending on the age of onset. In children, the syndrome is characterized by short stature with normal body proportions and reduced growth rate (dwarfism). A deficiency in growth hormone secretion in adult life may be characterized by excessive adiposity, reduced muscle mass, impaired exercise capacity, reduced body water, decreased bone mineral density, and psychological disorders. For example, a deficiency in growth hormone may result in myocardial dysfunction, in particular left ventricular diastolic dysfunction. M. Shahj, et al., Br. Heart J., 67, 92-96 (1992). A deficiency in growth hormone also has been suggested to be a factor in increased mortality from cardiovascular disease of adults with growth hormone-deficiency. T. Rosen, et al., Lancet, 336, 285-288 (1990).

Supplemental growth hormone administered for a four month period to growth hormone-deficient adults was reported to have no significant effect on left ventricular mass. J.O.L. Jorgensen, et al., Lancet, 1221-1225 (June 3, 1989); M. Shahj, et al., Br. Heart J., 67, 92-96 (1992). However, when administered to growth hormone-deficient adults over a six month period, supplemental growth hormone increased left ventricular mass, and provided favorable cardiovascular effects including increased cardiac output and glomerular filtration rate and reduced peripheral vascular resistance. K. Caldahl, et al., Clin. Endocrinol., 40, 393-400 (1994). In a patient suffering from growth hormone deficiency and poor cardiac function, supplemental growth hormone resulted in improvement in myocardial contractility and cardiac output. R.C. Cuneo, et al, Lancet, 1, 838-839 (1989). Supplemental growth hormone therapy

in growth hormone-deficient adults was found to improve resting and exercise cardiac function, but at the expense of ventricular hypertrophy. S. Fort, et al., Circulation, 90 (4, Part 2), pg. I-610, abs. 3290 (1994). Similarly, growth hormone replacement therapy in growth hormone-deficient adults increased exercise tolerance and improved left ventricular diasolic function without demonstrable changes in left ventricular mass, cardiac output, or peripheral resistance. S. Beshyah, et al., Eur. J. Endocrinol., 130, 451-458 (1994). In addition, forms of dilated cardiomyopathy in growth hormone-deficient adults may benefit from growth hormone replacement therapy. A. Frustaci, et al., Am. J. Clin. Path., 97, 503-511 (1992). The administration of growth hormone also improves serum lipids and lipoproteins in growth hormone-deficient adults. R.C. Cuneo, et al., Metabolism, 42(12), 1519-1523 (1993).

Although the effects of growth hormone in human heart failure patients without growth hormone deficiency have not been reported, in adult rats with postinfarction left ventricular dysfunction growth hormone treatment increased left ventricular systolic pressure and reduced end-diastolic pressure. R. Yang, et al., Cardiovasc. Drugs Ther., 9, 125-131 (1995) and R. Yang, et al., Circulation, 92(2), 262-267 (July 15, 1995). Similarly, the administration of human growth hormone resulted in a decrease in the incidence of ventricular aneurysms in rats with experimental myocardial infarctions. H. E. Castagnino, et al., Int'l J. Cardio., 35, 101-114 (1992).

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known growth hormone secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous

growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray. In addition, administration of exogenous growth hormone may result in side-effects, including edema.

Certain compounds have been developed which stimulate the release of endogenous growth hormone. Peptides which are known to stimulate the release of endogenous growth hormone include growth hormone releasing hormone, the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890, PCT Patent Pub. No. WO 89/07110, and PCT Patent Pub. No. WO 89/07111) and GHRP-2 (described in PCT Patent Pub. No. WO 93/04081), as well as hexarelin (J. Endocrinol Invest., 15(Suppl 4), 45 (1992)).

Other compounds possessing growth hormone secretagogue activity are disclosed in the following: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. ~~5,206,235~~; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No.

WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995). Additional compounds with growth hormone secretagogue activity are described herein.

SUMMARY OF THE INVENTION

The present invention is directed to the use of a compound which has the ability to stimulate the release of natural or endogenous growth hormone for the prevention and treatment of congestive heart failure in a warm-blooded animal. Accordingly, the present invention provides a method for the prevention and treatment of congestive heart failure in a warm-blooded animal comprising the administration of a growth hormone secretagogue. Included within the scope of the invention is a method for protecting cardiac structure and/or cardiac function comprising the administration of a growth hormone secretagogue. The present invention further provides a pharmaceutical composition for the prevention and treatment of congestive heart failure.

DESCRIPTION OF THE INVENTION

The present invention is directed to the use of a compound which has the ability to stimulate the release of natural or endogenous growth hormone for the prevention and treatment of congestive heart failure in a warm-blooded animal. In particular, the present invention provides a method for the prevention and treatment of congestive heart failure in a warm-blooded animal comprising the administration of a growth hormone secretagogue.

By the term "growth hormone secretagogue" is meant any exogenously administered compound or agent that directly or indirectly stimulates or increases the endogenous release of growth hormone in an animal, in particular, a human.

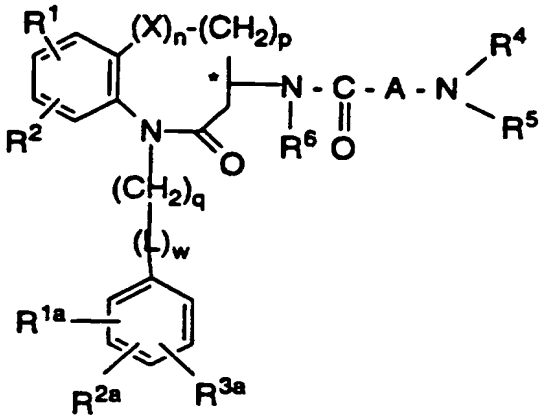
The growth hormone secretagogue may be peptidal or non-peptidal in nature, however, the use of a orally active growth hormone secretagogue is preferred.

The growth hormone secretagogue may be used alone or in combination with other growth hormone secretagogues or with other agents which are known to be beneficial in the prevention or treatment of hypertension or congestive heart failure. The growth hormone secretagogue and the other agent may be coadministered, either in concomitant therapy or in a fixed combination. For example, the growth hormone secretagogue may be administered in combination with an A_2-adenosine receptor agonist, α-adrenergic antagonist, angiotensin II antagonist, angiotensin converting enzyme inhibitor, β-adrenergic antagonist, antihypertensive, atriopeptidase inhibitor (alone or with ANP), calcium channel blocker, diuretic, potassium channel opening vasodilator, renin inhibitor, serotonin antagonist, and/or sympatholytic agent, as well as other antihypertensive agent.

Representative growth hormone secretagogues are disclosed in: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; EPO Patent Pub. No.

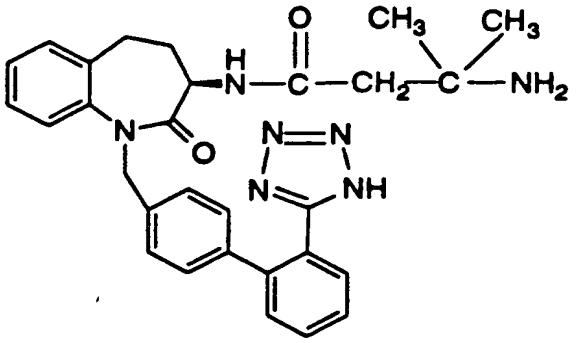
0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 89/07110; PCT Patent Pub. No. WO 89/07111; PCT Patent Pub. No. WO 93/04081; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; J. Endocrinol Invest., 15(Suppl 4), 45 (1992) ; Science, 260, 1640-1643 (1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995).

A representative first class of growth hormone secretagogues is set forth in U.S. Patent No. 5,206,235 as follows:

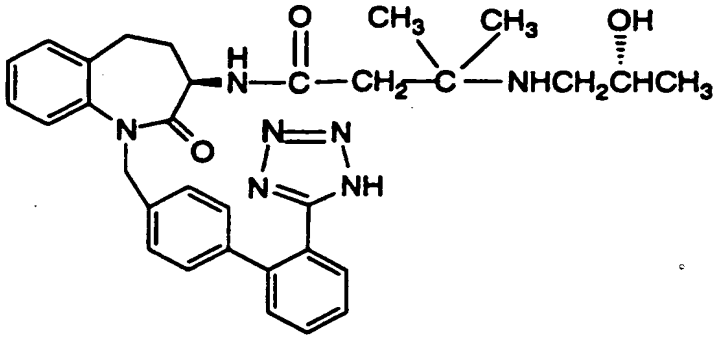


wherein the various substituents are as defined in U.S. Patent 5,206,235.

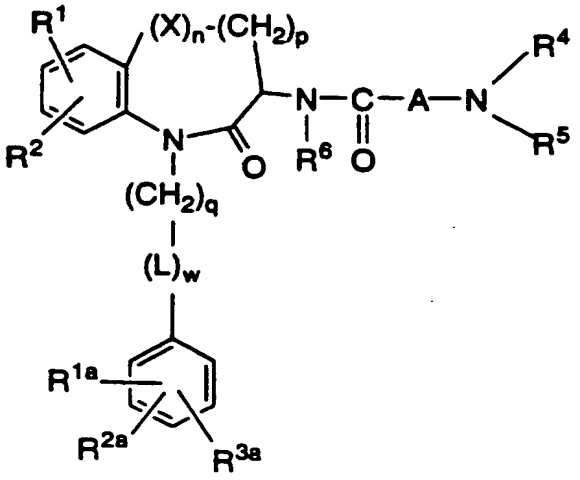
The most preferred compounds within this first class are identified as having the following structures:



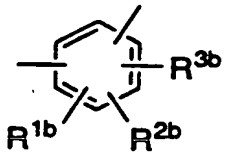
or



A representative second class of growth hormone secretagogues is set forth in U.S. Patent No. 5,283,241 and PCT Patent Publication No. 94/05634 as having the following structural formula:



wherein:
L is:



n is 0 or 1;
p is 0 to 3;
q is 0 to 4;
w is 0 or 1;

X is C=O, O, $S(O)_m$, $-\overset{OH}{\underset{|}{CH}}-$, $-\overset{R^{10}}{\underset{|}{N}}-$, or –CH=CH–;
m is 0 to 2;
R^1, R^2, R^{1a}, R^{2a}, R^{1b} and R^{2b} are independentl hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl, C_1-C_3 perfluoroalkoxy, $-S(O)_mR^{7a}$, cyano, nitro, $R^{7b}O(CH_2)_v$-, $R^{7b}COO(CH_2)_v$-, $R^{7b}OCO(CH_2)_v$, $R^4R^5N(CH_2)_v$-, $R^{7b}CON(R^4)(CH_2)_v$-, $R^4R^5NCO(CH_2)_v$-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy; R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy and v is 0 to 3;

R^{3a} and R^{3b} are independently hydrogen, R^9, C_1-C_6 alkyl substituted with R^9, phenyl substituted with R^9, or phenoxy substituted with R^9 with the proviso that either R^{3a} or R^{3b} must be a substituent other than hydrogen;

R^9 is $R^{4b}R^{12b}NCON(R^{12a})(CH_2)_v-$, $R^{4b}R^{12b}NCSN(R^{12a})(CH_2)_v-$, $R^{4b}R^{12c}NN(R^{12b})CSN(R^{12a})(CH_2)_v-$, $R^{4b}R^{12c}NN(R^{12b})CON(R^{12a})(CH_2)_v-$, $R^{4b}R^{12c}NN(R^{12b})COO(CH_2)_v-$, $R^{4b}R^{12b}NCOO(CH_2)_v-$, or $R^{13}OCON(R^{12a})(CH_2)_v-$, where v is 0 to 3;

R^{12a}, R^{12b} and R^{12c} are independently R^{5a}, OR^{5a}, or COR^{5a}; R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12a} and R^{12c}, or R^{12b} and R^{4b}, or R^{12c} and R^{4b}, or R^{13} and R^{12a} can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or NR^{10}, m is 0, 1 or 2, r and s are independently 0 to 3;

R^{13} is C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substitutents are hydroxy, $NR^{10}R^{11}$, carboxy, phenyl or substituted phenyl; phenyl or substituted phenyl where the substituents on the phenyl are selected from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or hydroxy;

R^4, R^{4b}, R^5 and R^{5a} are independently hydrogen, phenyl, substituted phenyl, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_3-C_{10} alkenyl, substituted C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, or substituted C_3-C_{10} alkynyl where the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, fluoro, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_{20}-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl or $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_1-C_6 alkyl, phenyl, phenyl C_1-C_6 alkyl, C_1-C_5-alkoxycarbonyl or C_1-C_5-alkanoyl-C_1-C_6 alkyl; or R^4 and R^5 can be taken together to form $-(CH_2)_r-B-(CH_2)_s-$ where B is CHR^1, O, $S(O)_m$ or $N-R^{10}$, r and s are independently 1 to 3 and R^1 and R^{10} are as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl, phenyl or phenyl C_1-C_{10} alkyl;

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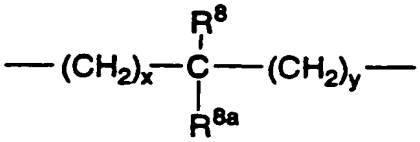
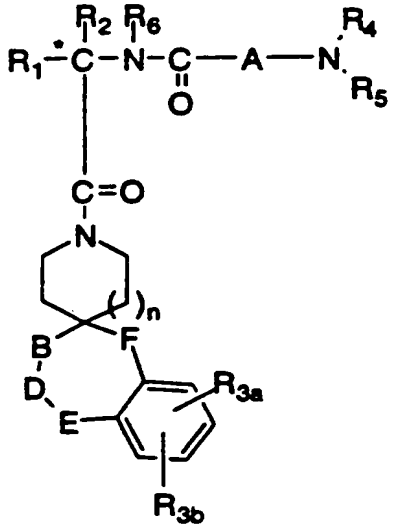


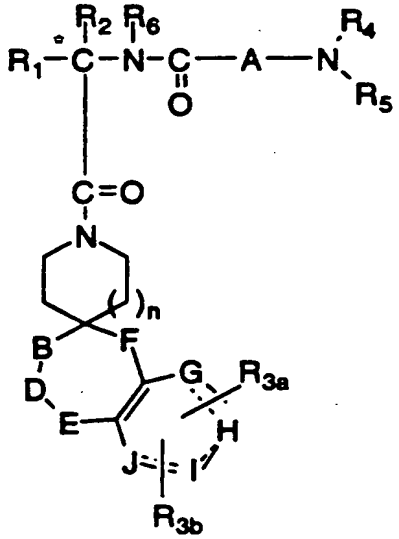
where x and y are independently 0-3;
R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl, trifluoromethyl, phenyl, substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, R^1, R^2 independently disubstituted phenyl C_1-C_3 alkoxy, R^1, R^2 independently disubstituted phenyl, C_1-C_5-alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, or $-NR^{10}R^{11}$ where R^{10} and R^{11} are as defined above; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 6; and R^8 and R^{8a} can independently be joined to one or both of R^4 and R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

The most preferred compound within this second class is identified as: 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)-carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide and pharmaceutically acceptable salts thereof, in particular, the hydrochloride salt thereof.

A representative third class of growth hormone secretagogues is disclosed in PCT Patent Pub. No. WO 94/13696 as compounds of the following structural Formulas I and II:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$, or -C≡C-,

and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:

hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a$ $(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

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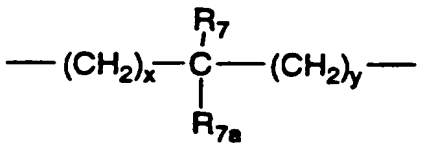
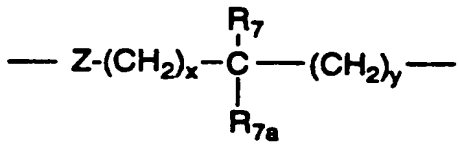


or



wherein x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

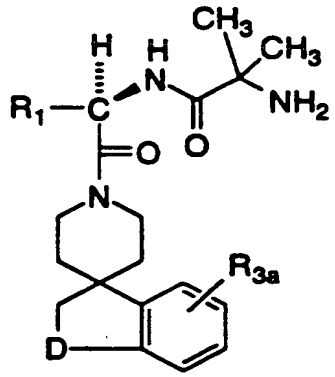
B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;
R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, -$(CH_2)_q$-aryl, -$(CH_2)_q$-$C(O)OR_2$, -$(CH_2)_q$-$C(O)O(CH_2)_q$-aryl, or -$(CH_2)_q$-(1H-tetrazol-5-yl), where the aryl may be

optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R9 is selected from the group consisting of:
-R_2, -$(CH_2)_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,
and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 -OR_{2a}, -$O(CH_2)_q$ aryl, 1 to 2 -$C(O)OR_{2a}$, 1 to 2 -$C(O)O(CH_2)_q$ aryl, 1 to 2 -$C(O)N(R_{2a})(R_{2a})$, 1 to 2 -$C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -$C(O)NHSO_2R_{2a}$, -$S(O)_mR_{2a}$, -$C(O)NHSO_2(CH_2)$q-aryl, -$SO_2NHC{\equiv}N$, -$SO_2NHC(O)R_{2a}$, -$SO_2NHC(O)(CH_2)_q$aryl, -$N(R_2)C(O)N(R_{2a})(R_{2a})$, -$N(R_{2a})C(O)N(R_{2a})(CH_2)_q$-aryl, -$N(R_{2a})(R_{2a})$, -$N(R_{2a})C(O)R_{2a}$, -$N(R_{2a})C(O)(CH_2)$q aryl, -$OC(O)N(R_{2a})(R_{2a})$, -$OC(O)N(R_{2a})(CH_2)_q$ aryl, -$SO_2(CH_2)_q$CONH-(CH_2)wNHC(O)R_{11},
wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

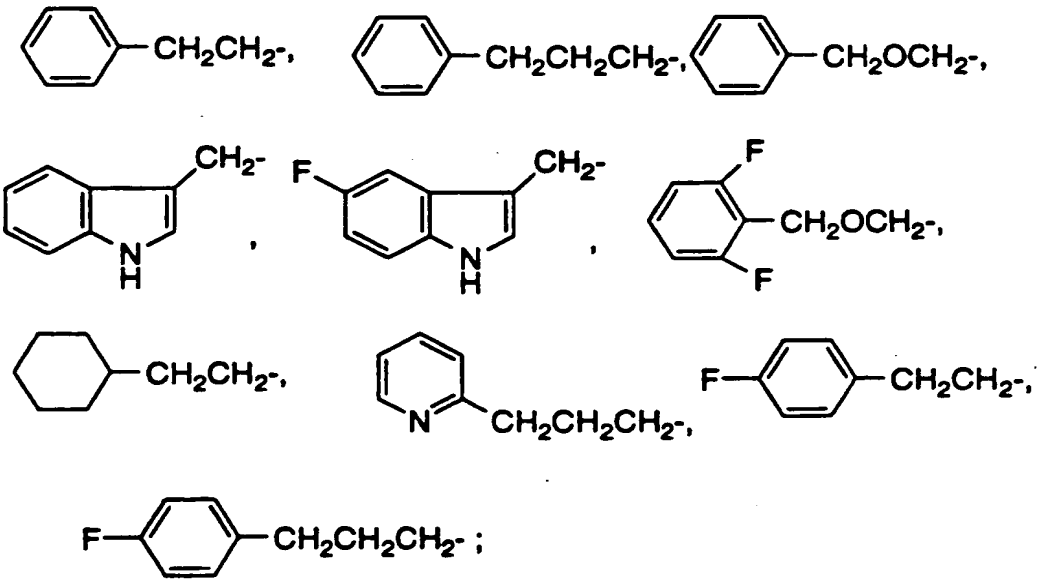
m is 0, 1 or 2;
n is 1, or 2;
q may optionally be 0, 1, 2, 3, or 4; and
G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring;
and pharmaceutically acceptable salts and individual diastereomers thereof.

Within this third class, the most preferred growth hormone secretagogues employed in the instant invention are realized in structural Formula V:



V

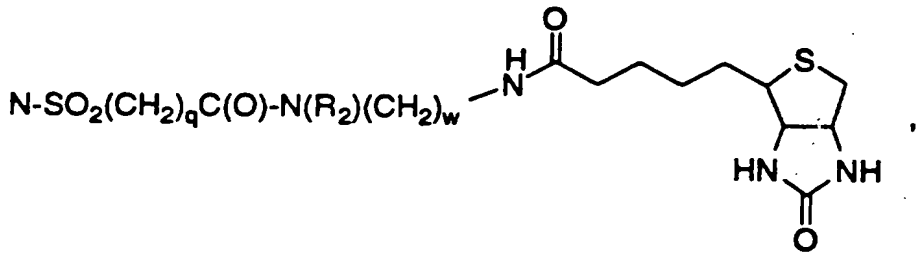
wherein R_1 is selected from the group consisting of:

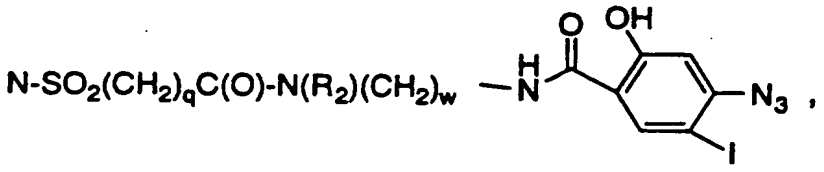


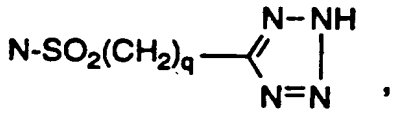
R_{3a} is H, or fluoro;

D is is selected from the group consisting of:

-O-, -S-, -S(O)m-, N(R2), $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $NSO_2(CH_2)_qC(O)$-$N(R_2)(R_2)$, N-$SO_2(CH_2)_qC(O)$-$N(R_2)(CH_2)_wOH$,







and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;

R_2 is H, or C_1-C_4 alkyl;
m is 1, 2;
t is 0, 1, or 2;
q is 1, 2, or 3;
w is 2, 3, 4, 5, or 6;
and the pharmaceutically acceptable salts and individual diastereomers thereof.

Representative most preferred growth hormone secretagoues within this third class which may be employed in the present invention include the following:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

Expecially preferred growth hormone secretagogues within this third class which may be employed in the present invention include:

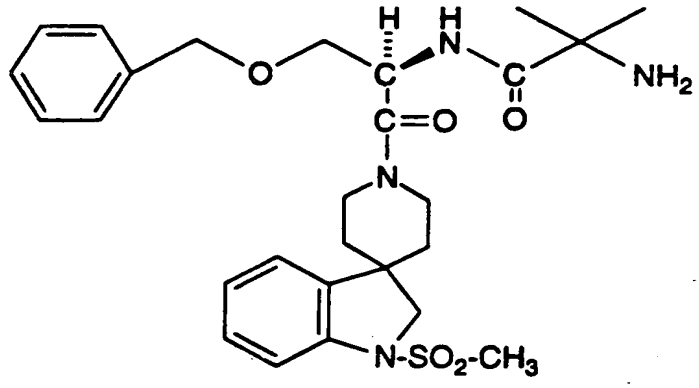
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

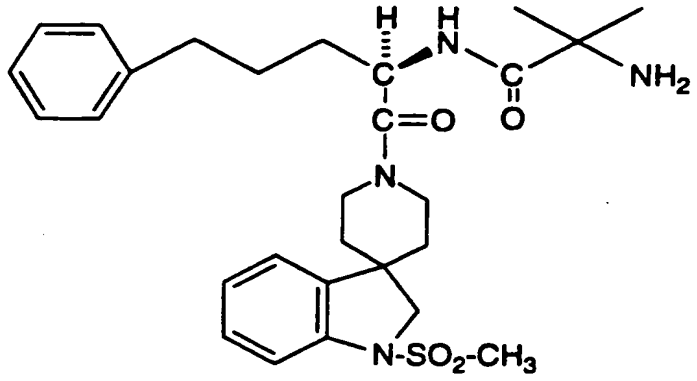
N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

and pharmaceutically acceptable salts thereof.

The most preferred compounds within this third class which may be employed in the present invention are identified as having the following structures:





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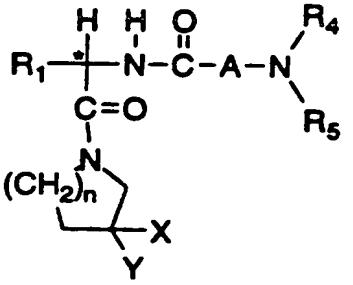
A representative fourth class of growth hormone secretagogues is disclosed in PCT Patent Publication WO 95/13069 as being compounds of the structural formula CI:



Formula CI

wherein:

R_1 is selected from the group consisting of:

C_1-C_{10} alkyl, aryl, aryl(C_1-C_6 alkyl), (C_3-C_7 cycloalkyl)(C_1-C_6 alkyl)-, (C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-, aryl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, where K is O, S(O)m, N(R_2)C(O), C(O)N(R_2), OC(O), C(O)O, -CR_2=CR_2-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R_2 and alkyl may be further substituted by 1 to 9 halogen, S(O)mR_{2a}, 1 to 3 of OR_{2a} or C(O)OR_{2a}, and aryl may be further substituted by 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of OR_2, methylenedioxy, -S(O)mR_2, 1 to 2 of -CF_3, -OCF_3, nitro, -N(R_2)C(O)(R_2), -C(O)OR_2, -C(O)N(R_2)(R_2), -1H-tetrazol-5-yl, -SO_2N(R_2)(R_2), -N(R_2)SO_2 phenyl, or -N(R_2)SO_2R_2;

R_2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR_{3a}, where R_{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl;

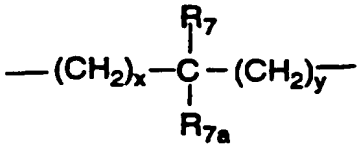
R_{2a} is hydrogen, or C_1-C_6 alkyl optionally substituted by hydroxyl;

X is selected from: hydrogen, -C≡N, -$(CH_2)_qN(R_2)C(O)R_2$, -$(CH_2)_qN(R_2)C(O)(CH_2)_t$aryl, -$(CH_2)_qN(R_2)SO_2(CH_2)_t$aryl, -$(CH_2)_qN(R_2)SO_2R_2$, -$(CH_2)_qN(R_2)C(O)N(R_2)(CH_2)_t$aryl, -$(CH_2)_qN(R_2)C(O)N(R_2)(R_2)$, -$(CH_2)_qC(O)N(R_2)(R_2)$, -$(CH_2)_qC(O)N(R_2)(CH_2)_t$aryl, -$(CH_2)_qC(O)OR_2$, -$(CH_2)_qC(O)O(CH_2)_t$aryl, -$(CH_2)_qOR_2$, -$(CH_2)_qOC(O)R_2$, -$(CH_2)_qOC(O)(CH_2)_t$aryl, -$(CH_2)_qOC(O)N(R_2)(CH_2)_t$aryl, -$(CH_2)_qOC(O)N(R_2)(R_2)$, -$(CH_2)_qC(O)R_2$, -$(CH_2)_qC(O)(CH_2)_t$aryl, -$(CH_2)_qN(R_2)C(O)OR_2$, -$(CH_2)_qN(R_2)SO_2N(R_2)(R_2)$, -$(CH_2)_qS(O)_mR_2$, and -$(CH_2)_qS(O)_m(CH_2)_t$aryl, where an R_2, $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted by 1 to 3 halogen, 1 to 3 -OR_2, -$CON(R_2)(R_2)$, -$C(O)OR_2$, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR_2$, or 1H-tetrazol-5-yl;

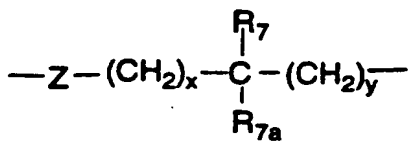
Y is selected from: hydrogen, C_1-C_{10} alkyl, -$(CH_2)_t$aryl, -$(CH_2)_q$(C_3-C_7 cycloalkyl), -$(CH_2)_q$-K-(C_1-C_6 alkyl), -$(CH_2)_q$-K-$(CH_2)_t$aryl, -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl containing O, NR2, S), and -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl), where K is O, $S(O)_m$, $C(O)NR_2$, CH=CH, C≡C, $N(R_2)C(O)$, $C(O)NR_2$, C(O)O, or OC(O), and where the alkyl, R_2, $(CH_2)_q$ and $(CH_2)_t$ groups may be optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, -$CONH_2$ or carboxylate C_1-C_4 alkyl esters, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1 to 3 halogen, 1 to 3 -OR_2, -$C(O)OR_2$, -$C(O)N(R_2)(R_2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR_2$, or 1H-tetrazol-5-yl, with the proviso that if X is hydrogen, Y is other than hydrogen;

R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenyloxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl), or R_4 and R_5 may be taken together to form $-(CH_2)_d$-$L_a(CH_2)_e$- where L_a is $-C(R_2)_2$-, O, $S(O)_m$ or $N(R_2)$, d and e are independently 1 to 3 and R_2 is as defined above;

A is:



or



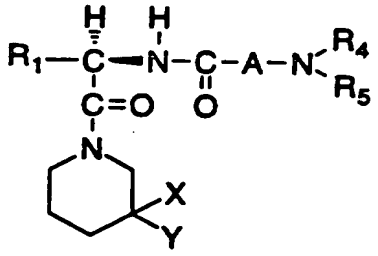
where x and y are independently 0, 1, 2 or 3;

Z is N-R_{6a} or O, where R_{6a} is hydrogen or C_1-C_6 alkyl;

R_7 and R_{7a} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR_2, $S(O)_mR_2$, $C(O)OR_2$, C_3-C_7 cycloalkyl, $N(R_2)(R_2)$, $C(O)N(R_2)(R_2)$, or R_7 and R_{7a} may independently be joined to one or both of R_4 and R_5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms, or R_7 and R_{7a} can be joined to one another to form C_3-C_7 cycloalkyl;

m is 0, 1, or 2;
n is 1, 2, or 3;
q is 0, 1, 2, 3, or 4;
t is 0, 1, 2, or 3;
and pharmaceutically acceptable salts and individual diastereomers thereof.

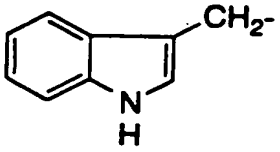
Representative preferred growth hormone secretagoues within this fourth class which may be employed in the present invention include those compounds of the structural Formula CIc:

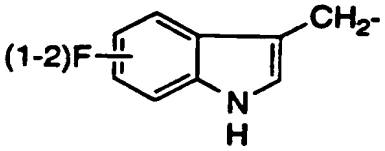


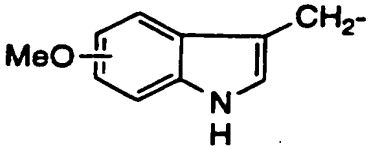
Formula CIc

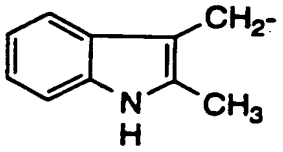
wherein:

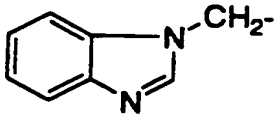
R_1 is selected from the group consisting of:

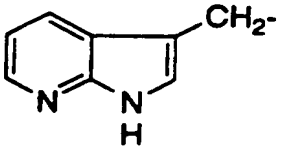


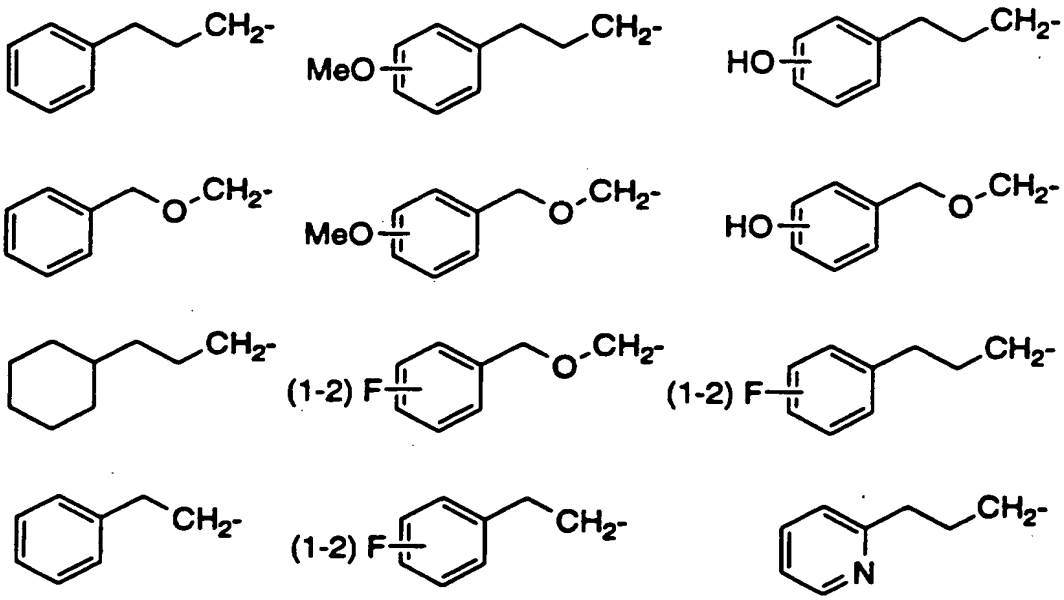






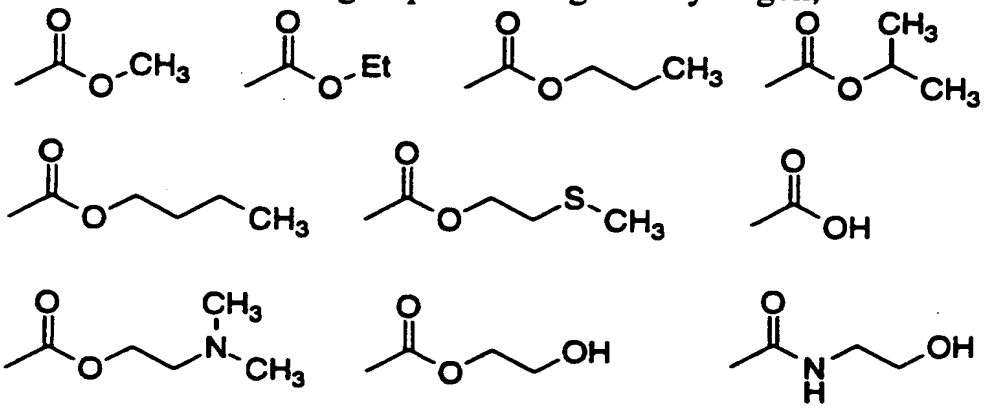


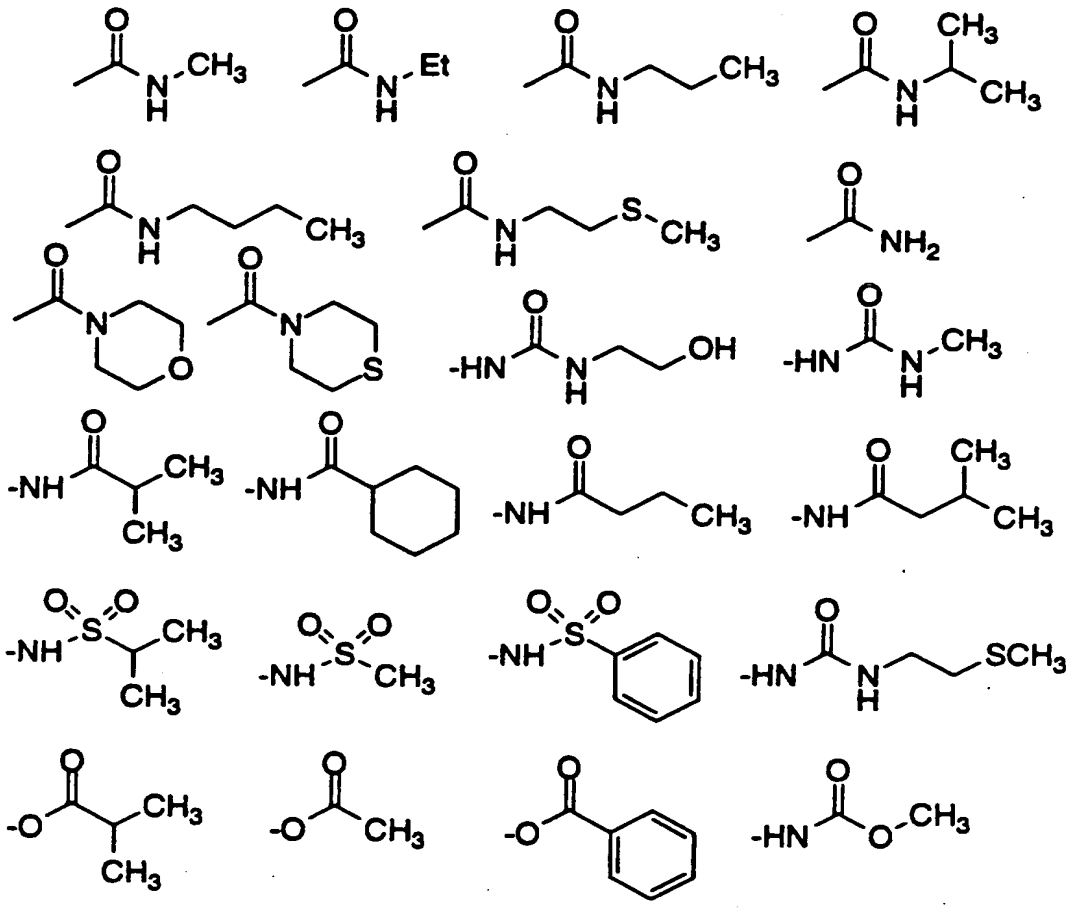




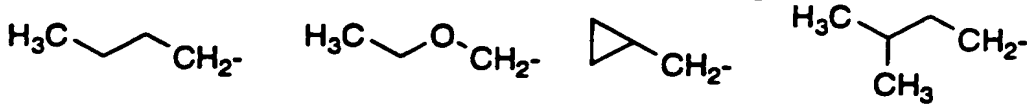
or their regioisomers where not specified;

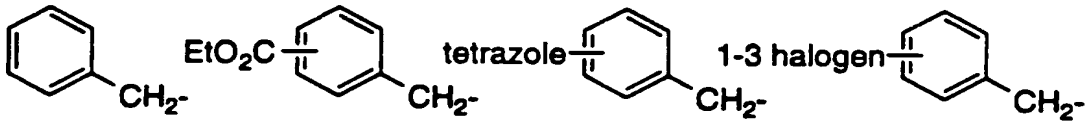
X is selected from the group consisting of: hydrogen,

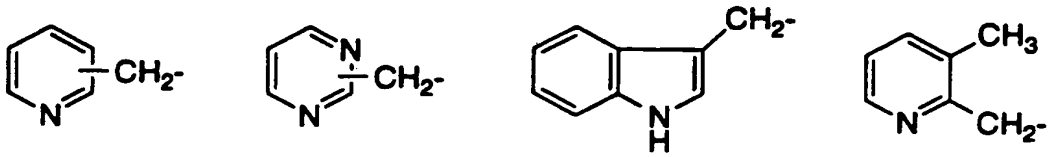


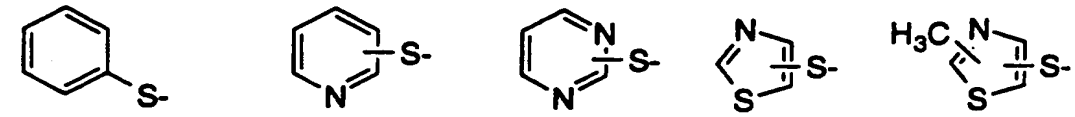


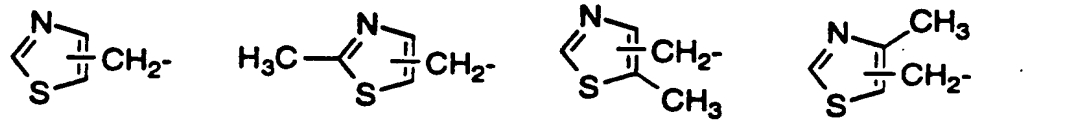
Y is selected from the group consisting of: hydrogen,

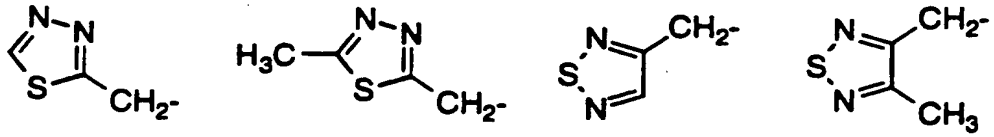


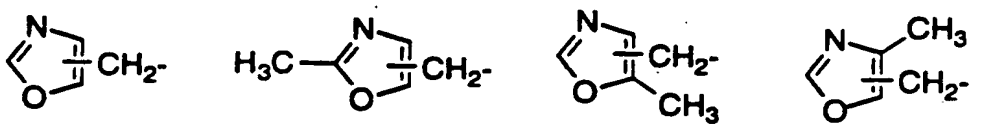


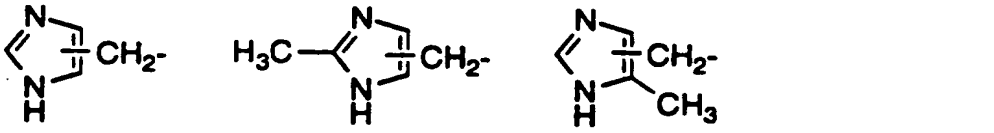


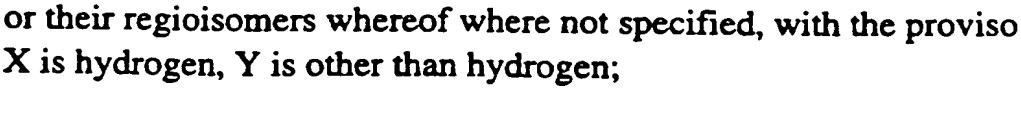






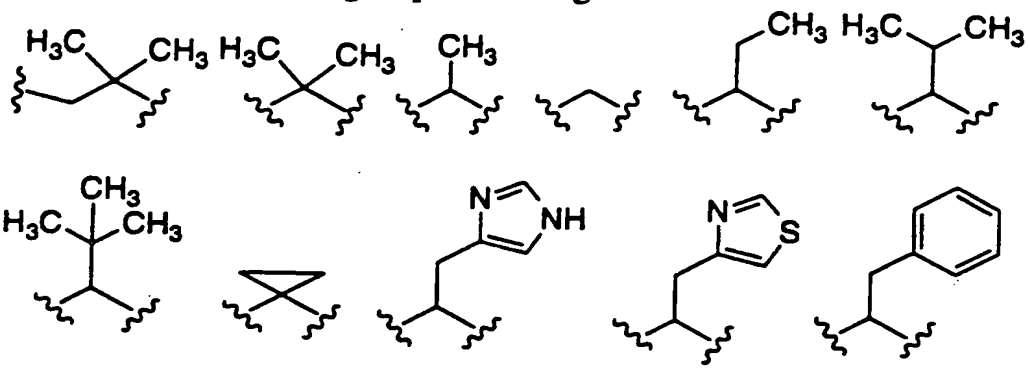




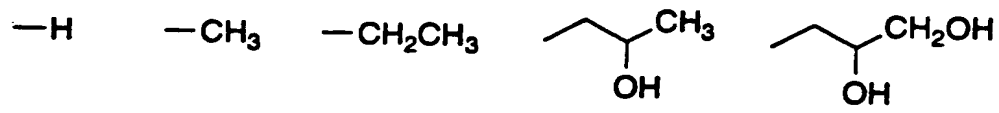


or their regioisomers whereof where not specified, with the proviso that if X is hydrogen, Y is other than hydrogen;

A is selected from the group consisting of:

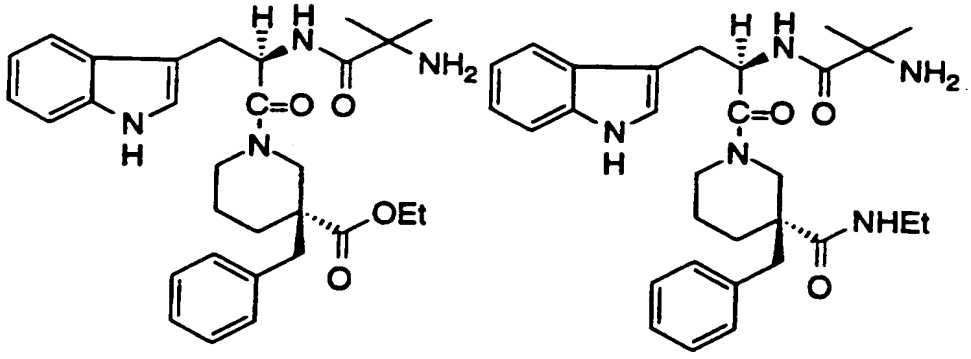


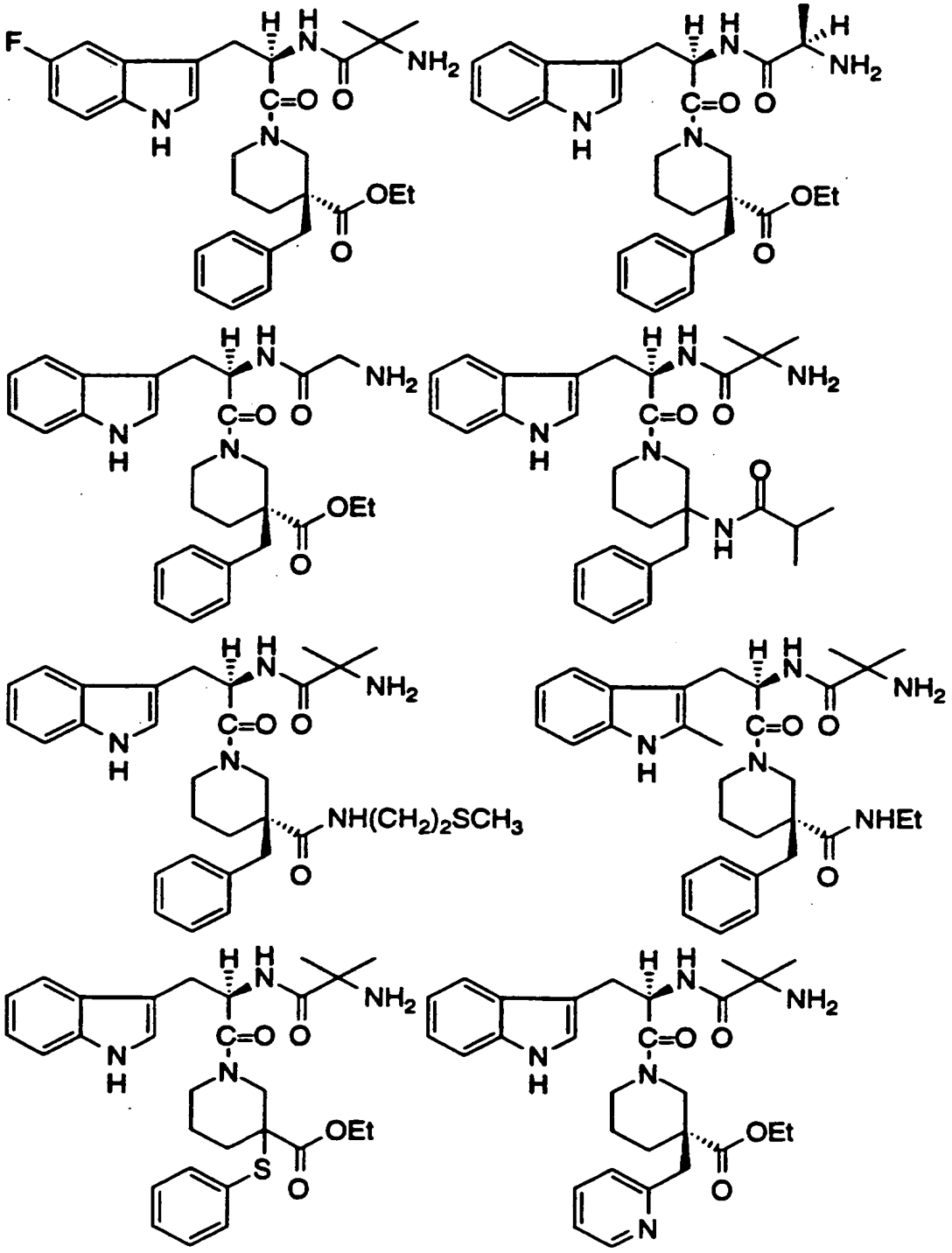
R4 and R5 are independently selected from the group consisting of:

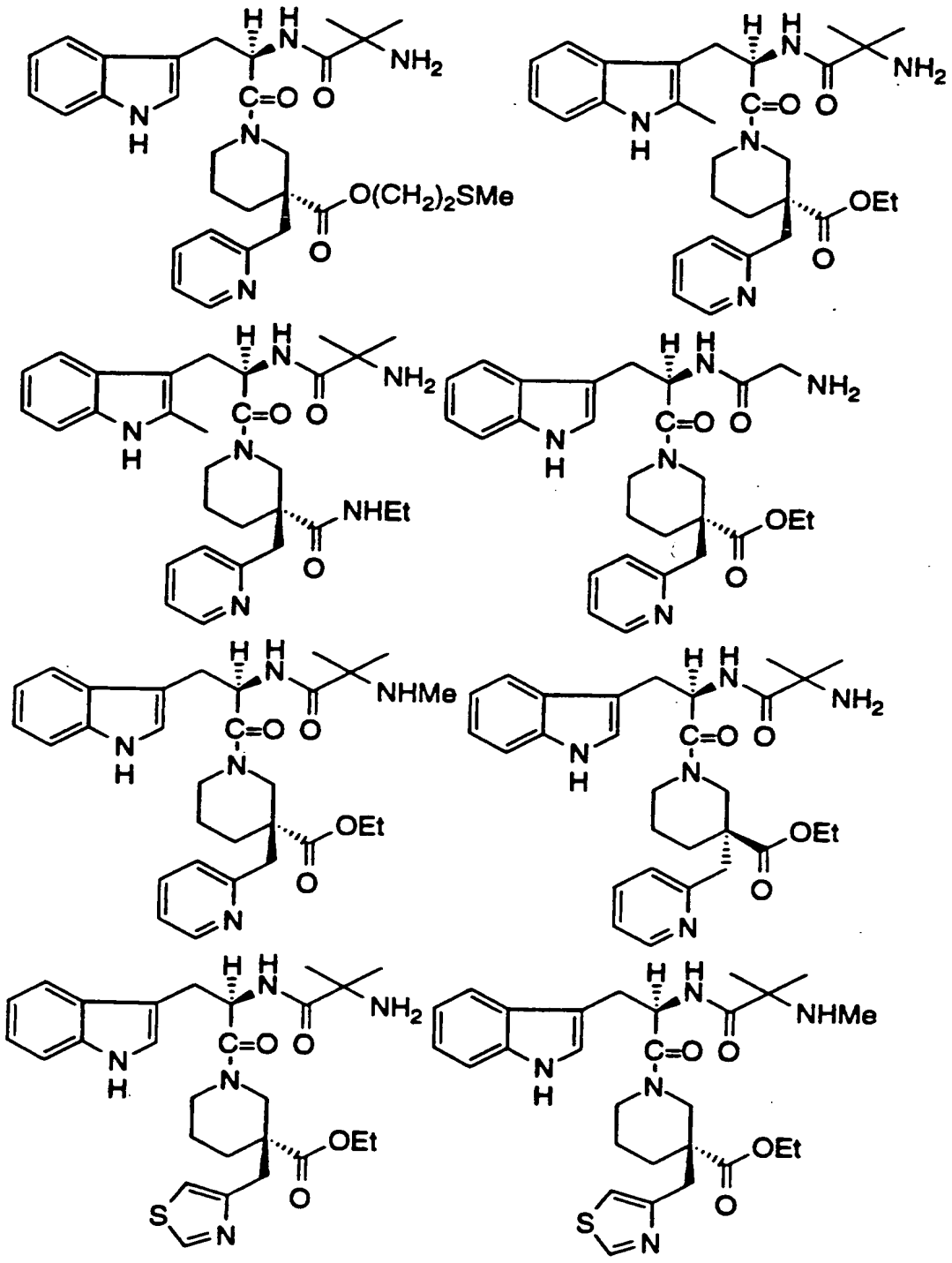


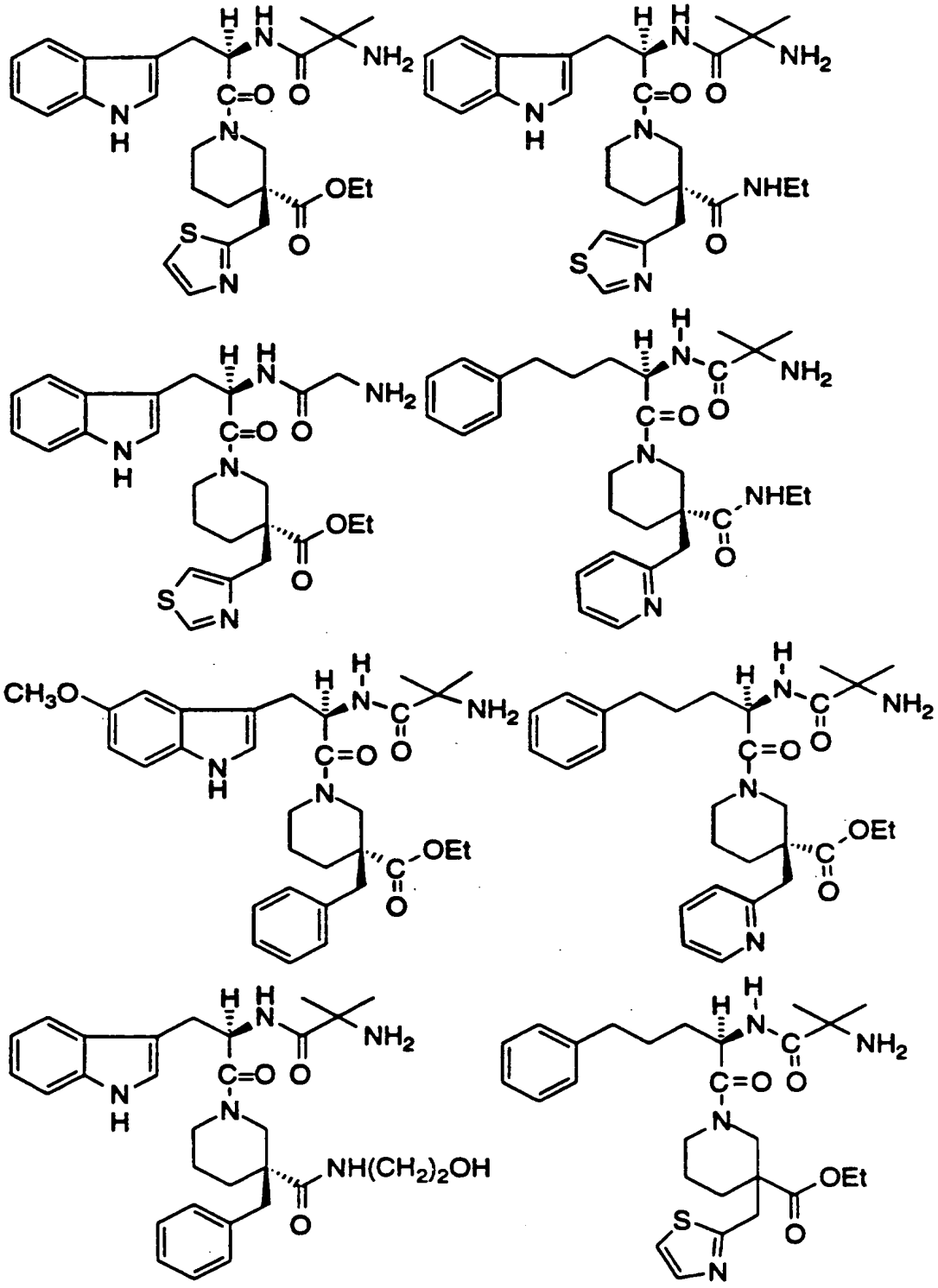
and pharmaceutically acceptable salts and individual diastereomers thereof.

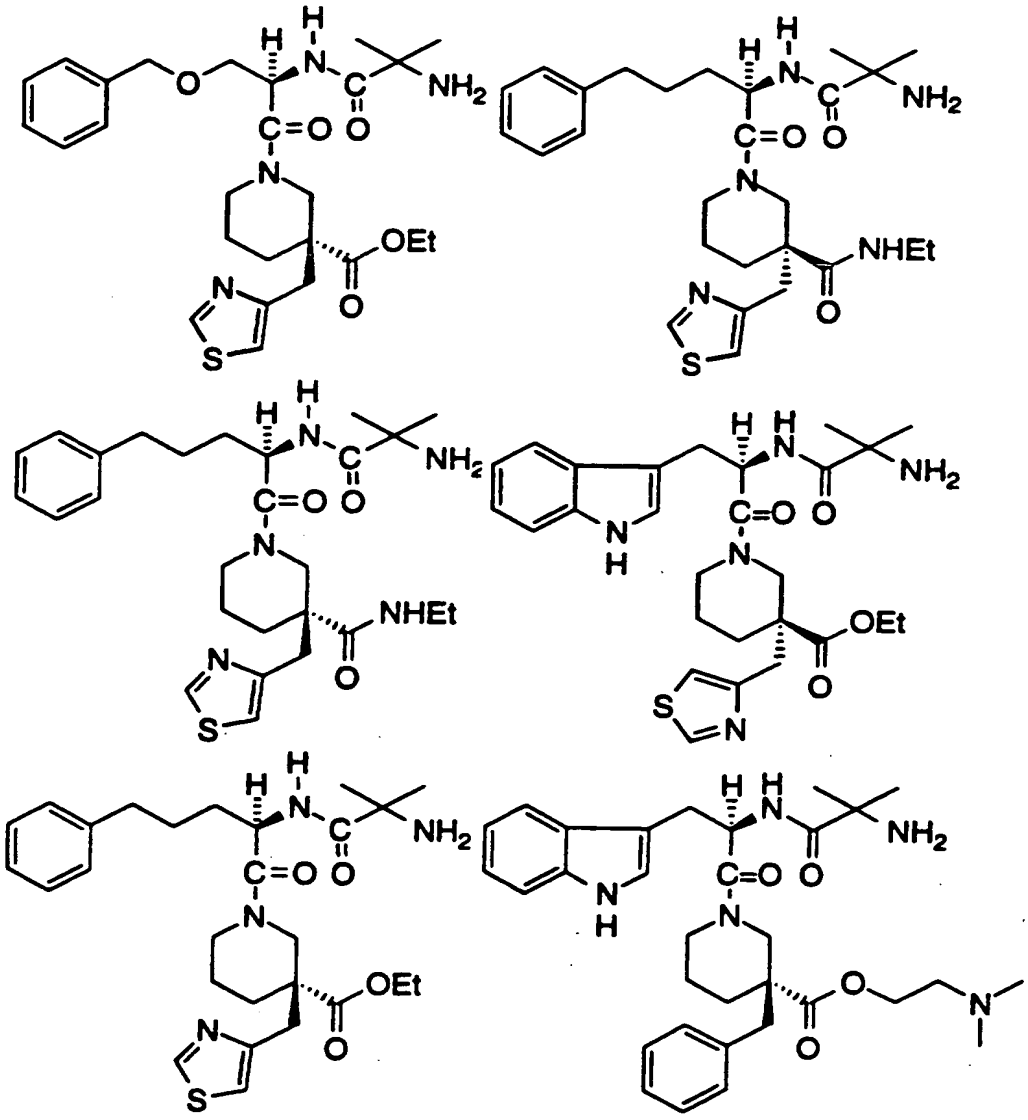
Representative most preferred growth hormone secretagoues within this fourth class which may be employed in the present invention include the following:




F
NH2
OEt
NH(CH2)2SCH3
NHEt
S
N

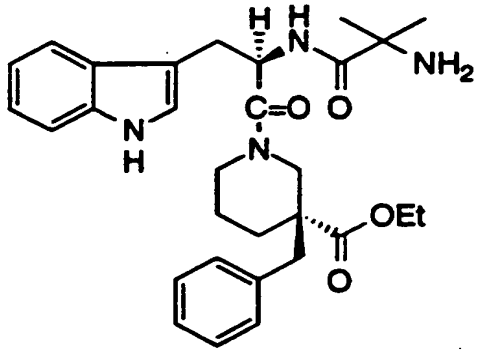






and their pharmaceutically acceptable salts and individual diasteromers thereof where not otherwise specified.

The most preferred growth hormone secretagoues within this fourth class which may be employed in the present invention include:



or a pharmaceutically acceptable salt thereof.

In the above structural formulas and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, ethinyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propenyl, butenyl, butadienyl and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propinyloxy, isobutenyloxy, 2-hexenyloxy, and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" is intended to include phenyl and naphthyl and aromatic residues of 5- and 6- membered rings with 1 to 3 heteroatoms or fused 5 or 6 membered bicyclic rings with 1 to 3 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic

aromatic rings are pyridine, thiophene, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, furan, pyrimidine, and thiadiazole.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other. Similarly, the use of a particular variable within a noted structural formula is intended to be independent of the use of such variable within a different structural formula.

Full descriptions of the preparation of the growth hormone secretagoue employed in the present invention may be found e.g., in: U.S. Patent No. 3,239,345; U.S. Patent No. 4,036,979; U.S. Patent No. 4,411,890; U.S. Patent No. 5,206,235; U.S. Patent No. 5,283,241; U.S. Patent No. 5,284,841; U.S. Patent No. 5,310,737; U.S. Patent No. 5,317,017; U.S. Patent No. 5,374,721; U.S. Patent No. 5,430,144; U.S. Patent No. 5,434,261; U.S. Patent No. 5,438,136; EPO Patent Pub. No. 0,144,230; EPO Patent Pub. No. 0,513,974; PCT Patent Pub. No. WO 94/07486; PCT Patent Pub. No. WO 94/08583; PCT Patent Pub. No. WO 94/11012; PCT Patent Pub. No. WO 94/13696; PCT Patent Pub. No. WO 94/19367; PCT Patent Pub. No. WO 95/03289; PCT Patent Pub. No. WO 95/03290; PCT Patent Pub. No. WO 95/09633; PCT Patent Pub. No. WO 95/11029; PCT Patent Pub. No. WO 95/12598; PCT Patent Pub. No. WO 95/13069; PCT Patent Pub. No. WO 95/14666; PCT Patent Pub. No. WO 95/16675; PCT Patent Pub. No. WO 95/16692; PCT Patent Pub. No. WO 95/17422; PCT Patent Pub. No. WO 95/17423; Science, 260, 1640-1643 (June 11, 1993); Ann. Rep. Med. Chem., 28, 177-186 (1993); Bioorg. Med. Chem. Ltrs., 4(22), 2709-2714 (1994); and Proc. Natl. Acad. Sci. USA 92, 7001-7005 (July 1995), as well as herein.

Methods to obtain the growth hormone releasing peptides GHRP-6 and GHRP-1 are described in U.S. Patent Nos. 4,411,890 and PCT Patent Publications WO 89/07110, WO 89/07111, methods to obtain the growth hormone releasing peptide GHRP-2 are described in PCT Patent Publication WO 93/04081, and methods to obtain hexarelin are described in J. Endocrinol Invest., 15(Suppl 4), 45 (1992).

The identification of a compound as a "growth hormone secretagogue" and thus able to directly or indirectly stimulate or increase the endogenous release of growth hormone in an animal may be readily determined without undue experimentation by methodology well known in the art, such as the assay described by Smith, *et al.*, *Science*, *260*, 1640-1643 (1993) (see text of Figure 2 therein). In a typical experiment pituitary glands are aseptically removed from 150-200 g Wistar male rats and cultures of pituitary cells are prepared according to Cheng et al. *Endocrinol.* , *124*, 2791-2798 (1989). The cells are treated with the subject compound and assayed for growth hormone secreting activity and intracellular cAMP levels as described by Chang et al. In particular, the intrinsic growth horomone secretagogue activity of a compounds which may be used in the present invention may be determined by this assay.

Accordingly, the present invention includes within its scope the use of a growth hormone secretagogue, alone or in combination with other agents, for the prevention or treatment of congestive heart failure in a warm-blooded animal. For the purposes of this disclosure, a warm-blooded animal is a member of the animal kingdom which includes but is not limited to mammals and birds. The preferred mammal for purposes of this invention is human.

Included within the scope of the present invention is the use of a growth hormone secretagogue for improving pulmonary function in a subject suffering from heart failure. The growth hormone secretagogue is useful in restoring systolic and diastolic function, as well as increasing myocardial contractility and decreasing peripheral total vascular resistance. Moreover, administration of the growth hormone secretagogue is useful in diminishing or preventing loss of body weight and also enhancing recovery following congestive heart failure.

This particular application of growth hormone secretagogues provides unexpected benefit relative to the administration of exogenous growth hormone. In particular, the growth hormone secretagogue has advantage of inducing less salt retention than exogenously administered growth hormone. In addition, the growth hormone secretagogue enhances the normal pulsitile releases of endogenous growth hormone

and thus is more likely to reproduce the natural pattern of endogenous growth hormone release. Growth hormone secregagogues which are orally active also have the benefit being able to be administered orally, rather than just intravenously, intraperitoneally or subcutaneously.

In addition, the present invention includes within its scope a pharmaceutical composition for the prevention or treatment of congestive heart failure comprising, as an active ingredient, at least one growth hormone secretagogues in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one growth hormone secretagogue or another composition which exhibits a different activity, e.g., an antibiotic growth promoting agent or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects. Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox. or peptides disclosed in U.S. Patent No. 4,411,890.

The present invention further includes the use of a growth hormone secretagogue in the manufacture of a medicament for the treatement of congestive heart failure.

In addition, the present invention contemplates the use of a growth hormone secretagogue for the treatment of congestive heart failure in combination with another growth hormone secretagogues such as those referenced herein, including the growth hormone releasing peptides GHRP-6 and GHRP-1 (described in U.S. Patent No. 4,411,890 and PCT publications WO 89/07110, WO 89/07111) and GHRP-2 (described in WO 93/04081) and B-HT920, as well as hexarelin or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs, or growth hormone and its analogs, or somatomedins including IGF-1 and IGF-2, or with α-adrenergic agonists such as

clonidine or serotonin 5HTD agonists such as sumatriptan, or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. For example, a growth hormone secretagogue may be used in combination with IGF-1 for the treatment or prevention of congestive heart failure.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to prevent or treat congestive heart failure. Combinations of these therapeutic agents some of which have also been mentioned herein with a growth hormone secretagogue will bring additional, complementary, and often synergistic properties to enhance the desirable properties of these various therapeutic agents. In these combinations, the growth hormone secretagogue and the therapeutic agents may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

The growth hormone secretagogue may be administered in combination with an A2-adenosine receptor agonists, α-adrenergic antagonist, angiotensin II antagonist, angiotensin converting enzyme inhibitor, β-adrenergic antagonist, antiarrhythnmic agent, antihypertensive, atriopeptidase inhibitor (alone or with ANP), β-blocker, calcium channel blocker, diuretic, digitalis, phosphodiesterase inhibitor, potassium channel opening vasodilator, renin inhibitor, sertonin antagonist, sympatholytic agent and/or a vasodialoator. For example, a growth hormone secretagogue may be given in combination with such compounds as: A-69729, acetazolamide, alacepril, altizide, amiloride, aminophylline, amrinone, azosemide, atenolol, atriopeptin, bendroflumethiazide, benzapril, benzclortriazide, benzthiazide, BIBR-277, butizide, candesartan, captopril, ceranopril, chlorothalidone, chlorothiazide, cilazapril, cilexetil, clonidine, cromakalim, cryptenamine acetates and cryptenamine tannates, CSG 22492C, cyclopenthiazide, cyclothiazide, delapril, deserpidine, diazoxide, digitalis, digoxin, diflusinal, diltiazem, dopamine, dobutamine, doxazosin, enalapril, enalaprilat, eprosartan, ethacrynic acid, ethiazide, felodipine, FK 744, FK 906, fosinopril, furosemide, guanabenz, guanethidine, guanethidine

sulfate, hydralazine hydrochloride, hydrochlorothiazide, hydroflumethiazide, idrapril, imidapril, irbesartan, isradipine, ketanserin, libenzapril, lisinopril, losartan, merethoxylline procaine, methylchlothiazide, metolazone, metoprolol, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, milrinone, minoxidil, moexipril, moveltopril, nadolol, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, nitroglycerine, nitroprusside, pargyline hydrochloride, penflutazide, pentopril, perindopril, pinacidil, pindolol, polythiazide, prazosin, prentyl, propranolol, quinapril, quinapril hydrochloride, quinethazone, ramapril, rauwolfia serpentina, rescinnamine, reserpine, SK&F-108566, sodium ethacrynate, sodium nitroprusside, spirapril, spironolactone, SR-47436, synecor, tasosartan, TCV-116, telmisartan, temocapril, teprotide, terazosin, ticrynafan, timolol maleate, triamterene, trichlormethazide, trandolopril, trichlormethiazide, trimethophan camsylate, UK-73900, utibapril, valsartan, verapamil, zabicipril, zalicipril, zofenopril, zofenopril calcium, zolasartan, and the like, as well as admixtures and combinations thereof.

Combinations useful in the management of congestive heart failure include, in addition, growth hormone secretagogues with cardiac stimulants such as dobutamine and xamoterol and phosphodiesterase inhibitors including amrinone and milrinone.

Typically, the individual daily dosages for these combinations may range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

To illustrate these combinations, a growth hormone secretagogue effective clinically effective clinically at a given daily dose range may be effectively combined, at levels which are equal or less than the daily dose range, with the following compounds at the indicated per day dose range: hydrochlorothiazide (6-200 mg), chlorothiazide (125-2000 mg), furosemide (5-80 mg), ethacrynic acid (5-200 mg), amiloride (5-20 mg), diltiazem (30-540 mg), felodipine(1-60 mg), nifedipine(5-120 mg), nitrendipine(5-60 mg), timolol maleate (1-60 mg), propanolol (10-

480 mg), an angiotensin II antagonist, such as losartan (2.5-250 mg, preferably 50 mg), and methyldopa (65-2000 mg).

In addition, triple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus losartan (5-20 mg); or triple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus amiloride (5-20 mg); or triple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus timolol maleate (5-60 mg); or triple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus nifedipine (5-60 mg) are effective combinations to control blood pressure in hypertensive patients. Similarly, quadruple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus amiloride (5-20 mg), plus an angiotensin II antagonist (3-200 mg); or quadruple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus timolol maleate (5-60 mg), plus an angiotensin II antagonist (0.5-250 mg); or quadruple drug combinations of a growth hormone secretagogue (1.0-100 mg), plus hydrochlorothiazide (15-200 mg), plus nifedipine (5-60 mg), plus an angiotensin II antagonist (0.5-250 mg) are also effective combinations to control blood pressure in hypertensive patients and/or provide benefit in the prevention or treatment of congestive heart failure. Naturally, these dose ranges may be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as oxymetholone, methyltesterone, fluoxymesterone and stanozolol.

These combinations may be formulated into pharmaceutical compositions as known in the art and as discussed below.

A growth hormone secretagogue may be administered alone or in combination by oral, parenteral (e.g., intramuscular, intraperitoneal,

intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. When the dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. Tablets and pills can additionally be prepared with enteric coatings and tablets may be coated with shellac, sugar or both.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions,

suspensions, or emulsions. Sterile compositions for injection may be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like may be incorporated as required. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax. Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The active ingredient may be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. . The dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth

hormone. The dosage range will generally be about 0.5 mg to 1.0 g. per patient per day which may be administered in single or multiple doses. Perferably, the dosage range will be about 0.5 mg to 500 mg per patient per day; more preferably about 0.5 mg to 200 mg per patient per day.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,

Step A: 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 9.22 g (45.6 mmol) of 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985)) in 30 mL methanol was hydrogenated at 40 psi in the presence of 1.0 g of 5% Pt/C for 4.5 hours. Celite was added and the mixture filtered through a pad of Celite. The filtrate was concentrated and allowed to stand for 16 hours at room temperature which resulted in formation of crystals. The material was isolated by filtration and dried under vacuum to afford 4.18 g (23.7 mmol, 52%) of the product. The mother liquors were diluted to 100 mL with methanol, treated with 2 g of charcoal, filtered through Celite and the filtrate concentrated under vacuum to approximatley 15 mL. A second crop formed yielding 2.02 g of product (11.5 mmol, 25%). Another recycling of the mother liquors afforded a third crop of 0.88 g (5.0, 11%). A total of 7.08 g (40.2 mmol, 88%) of the product was thus obtained. ^{1}H NMR (200 MHz, $CDCl_3$): 1.6 (br s, 2H), 1.80 (m, 1H), 2.55 (m, 2H), 2.88 (m, 1H), 3.42 (dd; 7Hz, 11Hz; 1H), 6.98 (d, 8Hz, 1H), 7.2 (m, 3H), 8.3 (br s, 1H). FAB-MS: calculated for $C_{10}H_{12}N_2O$ 176; found 177 (M+H, 100%).

Step B: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

2.37 g (13.5 mmol) of 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) and 2.02 g (13.5 mmol) of L-tartaric acid were suspended in 40 mL of ethanol. The mixture was gently heated and complete dissolution achieved by dropwise addition of 5 mL of distilled water. The solution was cooled to room temperature and aged overnight. The solid that formed was removed by filtration, washed with ethanol/diethyl ether (1:1) and dried under vacuum to afford 1.75 g of crude L-tartrate salt. The mother liquors were evaporated to dryness under vacuum, redissolved in 40 mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (6x20 mL) and the combined extracts washed with water (1x) and brine (1x), dried over potassium carbonate, filtered and solvents removed under vacuum to afford 1.29 g (7.33 mmol) of partially enriched 3(R) amine.

The original 1.75 g batch of L-tartrate salt was recrystallized twice from aqueous ethanol to afford 1.03 g (3.17 mmol, 24%) of purified L-tartrate salt with $[a]_D=-212°$ (c=1, H_2O). The purified L-tartrate salt was dissolved in 20 mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (5x10 mL); combined extracts were washed with water and brine then dried over potassium carbonate, filtered and solvents removed under vacuum to afford 522 mg (2.96 mmol, 22% overall) of the 3(S) amine, $[a]_D=-446°$ (c=1,CH_3OH).

The remaining 1.29 g (7.33 mmol) of partially enriched 3(R) amine was treated with 1.10 g (7.33 mmol) of D-tartaric acid as described above and the resulting salt recrystallized twice from aqueous ethanol to afford 1.20 g of purified D-tartrate salt, $[a]_D=-214°$ (c=1,H_2O). The purified D-tartrate salt was dissolved in 20 mL of water and the free base isolated as described above to give 629 mg (3.57 mmol, 26% overall) of the 3(R) amine, $[a]_D=+455°$ (c=1,CH_3OH).

Step C: 2,2-Dimethylbutanedioic acid, 4-methyl ester

2,2-dimethylsuccinic acid (20 g, 137 mmol) dissolved in 200 mL absolute methanol at 0°C was treated dropwise with 2 mL

concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 16 hours.

The mixture was concentrated *in vacuo* to 50 mL and slowly treated with 200 mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6N HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed *in vacuo*. The residue was dried at room temperature under vacuum to afford 14.7 g (91.8 mmol, 67%) of a viscous oil that slowly solidified upon standing. ^{1}H NMR analysis indicates the product is a mixture of the title compound and 15% of the isomeric 2,2-dimethylbutanedioic acid, 1-methyl ester. NMR (200 MHz, $CDCl_3$) of title compound: 1.29 (s, 6H), 2.60 (s, 2H), 3.66 (s, 3H). NMR (200 MHz, $CDCl_3$) of isomer: 1.28 (s, 6H), 2.63 (s, 2H), 3.68 (s, 3H).

Step D: 3-[Benzyloxycarbonylamino]-3-methylbutanoic acid, methyl ester

To 14.7 g (91.8 mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester (Step C), containing 15% of the isomeric 1-methyl ester compound, in 150 mL benzene was added 13 mL of triethylamine (9.4 g, 93 mmol, 1.01 eq) followed by 21.8 mL diphenylphosphoryl azide (27.8 g, 101 mmol, 1.1 eq). The mixture was heated under nitrogen at reflux for 45 minutes then 19 mL (19.9 g, 184 mmol, 2 eq) of benzyl alcohol was added and refluxing continued for 16 hours.

The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250 mL ethyl acetate, washed with water (1x), saturated aqueous sodium bicarbonate (2x) and brine (1x). The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume *in vacuo*. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27 g (68.9 mmol, 75%) of the title compound as a pale yellow liquid in addition to a small amount of pure 3-

[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester. ^{1}H NMR (200MHz, $CDCl_3$) of title compound: 1.40 (s, 6H), 2.69 (s, 2H), 3.63 (s, 3H), 5.05 (s, 2H), 5.22 (br s, 1H), 7.32 (s, 5H). ^{1}H NMR (200 MHz, $CDCl_3$) of 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (200 MHz, $CDCl_3$): 1.19 (s, 6H), 3.30 (d, 7Hz, 2H; resonance collapses to singlet in CD_3OD), 3.67 (s, 3H), 5.09 (s, 2H), 5.22 (br s,1H; resonance not observed in CD_3OD), 7.3 (br s, 5H).

Step E: 3-Benzyloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27 g (68.9 mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate (Step D) in 20 mL of methanol at room temperature was treated dropwise with 51 mL of 2N NaOH (102 mmol, 1.5 eq). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to 0°C and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26 g (68.7 mmol, 99%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.42 (s, 6H), 2.77 (s, 2H), 5.06 (s, 2H), 5.2 (br s, 1H), 7.3 (s, 5H).

Step F: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 252 mg (1.43 mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Step B) in 4 mL of methylene chloride at room temperature was added 400 mg (1.60 mmol, 1.1 eq) of 3-benzyloxycarbonylamino-3-methylbutanoic acid (Step E) followed by 760 mg (1.7 mmol, 1.2 eq) benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluoro-phosphate and 0.50 mL of diisopropyl-ethylamine (380 mg, 2.9 mmol, 2 eq). After 3 hours at room temperature, the mixture was diluted into 30 mL of ethyl acetate and washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate (2x) and brine.

The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 586 mg (1.43 mmol, 100%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.39 (s, 3H), 1.82 (m, 1H), 2.52 (s, 2H), 2.5-3.0 (m, 3H), 4.51 (m, 1H), 5.07 (br s, 2H), 5.57 (br s, 1H), 6.68 (d, 7Hz, 1H), 6.97 (d, 8Hz, 1H), 7.1-7.4 (m, 8H), 7.61 (br s, 1H). FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 (M+H, 100%); $[a]_D$=+137° (c=1, $CHCl_3$).

Step G: 5-Phenyltetrazole

Zinc chloride (3.3 g, 24.3 mmol, 0.5 eq) was added to 15 mL of N,N-dimethylformamide in small portions while maintaining the temperature below 60°C. The suspension of zinc chloride was cooled to room temperature and treated with 5.0 g of benzonitrile (48.5 mmol, 1.0 eq) followed by 3.2 g of sodium azide (48.5 mmol, 1.0 eq). The heterogeneous mixture was heated at 115°C with agitation for 18 hours. The mixture was cooled to room temperature, water (30 mL) was added and the mixture acidified by the addition of 5.1 mL of concentrated hydrochloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15 mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38 g (43.7 mmol, 90%) of the product.

Step H: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0 g (34.2 mmol) of 5-phenyltetrazole in 55 mL of acetone was added 5.0 mL of triethylamine (3.6 g, 35.6 mmol, 1.04 eq). After 15 minutes, a solution of 10.0 g of triphenyl-methyl chloride (35.9 mmol, 1.05 eq) in 20 mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour. Water (75 mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75 mL of water and dried at 60°C under vacuum to give 13.3 g (34.2 mmol, 100%) of the product.

Step I: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole

A solution of zinc chloride (6.3 g, 46.2 mmol, 0.6 eq) in 35 mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0 g, 77.3 mmol, 1.0 eq) was dissolved in 300 mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to -15°C and treated slowly with 50.5 mL of 1.6 M n-butyllithium in hexane (80.0 mmol, 1.05 eq) so as to maintain the temperature below -5°C. The solution was maintained at -5 to -15°C for 1.5 hours then treated with the dried zinc chloride solution and allowed to warm to room temperature.

In a separate flask, 4-iodotoluene (20.17 g, 92.5 mmol, 1.2 eq) and bis-(triphenylphosphine)nickel (II) dichloride (1.5 g, 2.3 mmol, 0.03 eq) were dissolved in 60 mL of tetrahydrofuran, then degassed and left under an atmosphere of nitrogen. The mixture was cooled to 5°C and treated with 1.5 mL of 3.0 M solution of methylmagnesium chloride in tetrahydrofuran (4.5 mmol, 0.06 eq) so as to keep the temperature below 10°C. The solution was warmed to room temperature and added, under nitrogen purge, to the arylzinc solution. The reaction mixture was stirred vigorously for 8 hours at room temperature then quenched by the slow addition of a solution of 10 mL of glacial acetic acid (1.6 mmol, 0.02 eq) in 60 mL of tetrahydrofuran at a rate so that the temperature was maintained below 40°C. The mixture was stirred for 30 minutes and 150 mL of 80% saturated aqueous sodium chloride was added; the reaction mixture was extracted for 30 minutes and the layers allowed to separate. The organic layer was removed and washed with 150 mL of 80% saturated aqueous sodium chloride buffered to pH>10 by the addition of ammonium hydroxide. The organic phase was removed and concentrated under vacuum to approximately 50 mL then 250 mL of acetonitrile was added. The mixture was again concentrated under vacuum to 50 mL and acetonitrile added to make the final volume 150 mL. The resulting slurry was cooled at 5°C for 1 hour then filtered and washed with 50 mL of cold acetonitrile followed by 150 mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for

12 hours to afford 30.0 g (62.8 mmol, 81%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 2.28 (s, 3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (m, 1H).

Step J: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole

A solution of 3.15 g (6.6 mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole (Step I) in 25 mL of methylene chloride was treated with 1.29 g (7.25 mmol, 1.1 eq) of N-bromo-succinimide, 80 mg (0.5 mmol, 0.07 eq) of AIBN, 200 mg of sodium acetate and 200 mg of acetic acid. The mixture was heated at reflux for 2 to 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued until almost all the methylene chloride was removed the the total volume reduce to approximately 12 mL and 12 mL of hexanes was then added. The mixture was kept at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81g (5.04 mmol, 76%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 4.38 (s, 2H), 6.9-8.0 (m, 23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

Step K: 3-Benzyloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 437 mg (1.07 mmol) of the intermediate obtained in Step F in 2 mL of dry dimethylformamide at room temperature under nitrogen was added 55 mg of 60% sodium hydride oil dispersion (33 mg NaH, 1.38 mmol, 1.3 eq). After 15 minutes, a solution of 715 mg (1.28 mmol, 1.2 eq) N-triphenyl-methyl-5-[2-(4'-

bromomethylbiphen-4-yl)] tetrazole (Step J) in 1.5 mL of dry dimethylformamide was added and the mixture stirred for 90 minutes.

The reaction mixture was added to 100 mL of ethyl acetate and washed with water (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1), afforded 902 mg (1.02 mmol, 95%) of the product. ^{1}H NMR (200 MHz, $CDCl_3$): 1.38 (s, 3H), 1.39 (s, 3H), 1.68 (m, 1H), 2.2-2.5 (m, 5H), 4.44 (m, 1H), 4.67 (d, 14Hz, 1H), 5.06 (s, 2H), 5.12 (d, 14Hz, 1H), 5.63 (br 1, 1H), 6.65 (d, 8Hz, 1H), 6.9-7.5 (m, 31H), 7.85 (m, 1H).

Step L: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 902 mg (1.02 mmol) of the intermediate obtained in Step H in 5 mL methanol was hydrogenated at room temperature and one atmosphere over 160 mg of 20% $Pd(OH)_2/C$ for 14 hours. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over 10 minutes) to afford 568 mg (0.91 mmol, 89%) of the title compound. ^{1}H NMR (200 MHz, CD_3OD): 1.33 (s, 3H), 1.37 (s, 3H), 2.0-2.6 (m, 6H), 4.35 (dd; 7, 11 Hz; 1H), 4.86 (d, 15 Hz, 1H), 5.20 (d, 15 Hz, 1H), 7.00 (d, 8 Hz, 2H), 7.15-7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS: calculated for $C_{29}H_{31}N_7O_2$ 509; found 510 (M+H, 100%).

EXAMPLE 2

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

Step A: 3-[(2-(R)-Benzyloxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate (Example 1) and (R)-2-benzyloxlpropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett., 26, 1261-1264 (1985) by the procedure described in U.S. Patent No. 5,206,235, Example 86, Step A. ^{1}H NMR (200MHz, CD_3OD): 1.25 (d, 6Hz, 3H), 1.35 (s, 6H), 2.11 (m, 1H), 2.32 (m, 1H), 2.5-2.7 (m, 4H), 2.95 (m, 1H), 3.17 (m, 1H), 3.80 (m, 1H), 4.40 (m, 1H), 4.44 (d, 11Hz, 1H), 4.64 (d, 11Hz, 1H), 4.90 (d, 15Hz, 1H), 5.02 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.1-7.7 (m, 15H). FAB-MS: calculated for $C_{39}H_{43}N_7O_3$ 657; found 658 (M+H, 100%).

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in U.S. Patent No. 5,206,235, Example 86, Step B. ^{1}H NMR (400MHz, CD_3OD): 1.22 (d, 6Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 2.10 (m, 1H), 2.31 (m, 1H), 2.45-2.70 (m, 4H), 2.81 (dd; 10, 12Hz; 1H), 3.08 (dd; 4, 12Hz; 1H), 3.92 (m, 1H), 4.36 (dd; 7, 11Hz; 1H), 4.93 (d, 15Hz, 1H), 5.17 (d, 15Hz, 1H), 7.04 (d, 8Hz, 2H), 7.19 (d, 8Hz, 2H), 7.20-7.35 (m, 4H), 7.54 (m, 2H), 7.65

(m, 2H). FAB-MS: calculated for $C_{32}H_{37}N_7O_3$ 567; found 568 (M+H, 45%).

EXAMPLE 3

2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)-carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide, hydrochloride

Step A: 1-Tetralone oxime

To 4.6 L of water at room temperature in a 4-neck 50 L flask sitting in a steam bath apparatus equipped with an overhead stirrer, a temperature probe and reflux condenser was added 3.72 Kg (27.36 mol) of sodium acetate with stirring, followed by 1.9 Kg of hydroxylamine hydrochloride (27.36 mol). To this slurry at room temperature, 12 L of ethanol was added followed by 1.994 Kg (13.68 mol) of 1-tetralone. Additional ethanol (1.7 L) was used to rinse off the funnel and added to the reaction mixture. The resulting light orange slurry was heated to 75°C over 40 minutes and maintained at 75-85°C for another 75 minutes. The reaction mixture was cooled with the aid of ice packed around the flask. When the internal temperature reached 32°C, the reaction mixture was pumped over 15 minutes into 60 L of ice contained in a 200 L vessel. The reaction vessel was washed with an additional 2 L of water which was added to the 200 L vessel. When the ice melted, the mixture was filtered through a filter pad and the wet cake washed with 4 L of water. The wet cake was suction dried for 1 hour then transferred to two trays and dried under vacuum at 40°C for 2 days to give 2.094 Kg (13.01 mol, 95%) of product. ^{1}H NMR (250 MHz, CDCl3): δ 1.90 (m, 2H), 2.80 (t, 6Hz, 2H), 2.88 (t, 6Hz, 2H), 7.15-7.35 (m, 3H), 7.90 (d, 8Hz, 1H), 8.9 (br s, 1H).

Step B: 2,3,4,5-Tetrahydro-1*H*-1-benzazepin-2-one

To 10 L of methanesulfonic acid in a 22 L 3-neck flask equipped with an overhead stirrer, a temperature probe, nitrogen inlet and reflux condenser, was added 2.6 Kg (18.61 mol) of phosphorus

pentoxide. An additional 1.6 L of methanesulfonic acid was used to wash all the phosphorus pentoxide into the vessel. The mixture was heated at 90°C for 2.5 hours then cooled to 50°C using an ice bath and treated with 2.00 Kg (12.41 mol) of 1-tetralone oxime in several portions over 15 minutes. The mixture was heated at 63°C for 10 minutes then slowly heated to 80°C and kept at 80°C for 3 hours. The reaction mixture was pumped into 70 L of ice then treated slowly with 11.25 L of 50% aqueous sodium hydroxide over 90 minutes at such a rate so as to maintain the temperature below 28°C. The mixture was filtered and 4 L of the filtrate was used to rinse the vessel. The wet cake (pink) was washed with 8 L of water then suction dried for 45 minutes and transferred to two trays and dried under vacuum at 40°C for 2 days to give 1.9 Kg (11.79 mol,95%) of product. ^{1}H NMR (250 MHz,CDCl3): δ 2.24 (m, 2H), 2.38 (t, 6Hz, 2H), 2.82 (t, 6Hz, 2H), 7.03 (d, 8Hz, 1H), 7.13 (m, 1H), 7.24 (m, 2H), 8.63 (br s, 1H).

Step C: 3-Iodo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one

A suspension of 1.8 Kg (11.17mol) of 2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one in a mixture of 22.33 L of methylene chloride and 11.78 L (55.83 mol) of hexamethyldisilazane was heated at reflux for 10 minutes, then cooled to 30°C and treated with 8.503 Kg (33.5 mol) of iodine in one portion. The mixture was heated at reflux for 2.5 hours, then cooled to room temperature. Aqueous sodium sulfite containing 4.926 Kg of sodium sulfite in 44 L of water was cooled to 0°C and into it was poured the reaction mixture in several portions with vigorous stirring while maintaining the temperature below 10°C. The reaction vessel was rinsed with 22.33 L of methylene chloride and the washing transferred to the quenching mixture. The quenching mixture was stirred vigorously and the layers allowed to separate. The aqueous layer was removed and reextracted with 22.33 L of methylene chloride. The combined organic layers were washed with 11 L of water and concentrated under vacuum to a final volume of approximately 5 L. The residue was treated with 55 L of toluene and concentrated under vacuum to a final volume of 10 L. The resulting slurry was isolated by filtration and the filter cake washed with

an additional 5 L of toluene and dried under vacuum at ambient temperature for 24 hours to give 1.842 Kg (6.42 mol, 57%) of product. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.6-2.8 (m, 3H), 2.93 (m, 1H), 4.64 (t, 8Hz, 1H), 6.97 (d, 8Hz, 1H), 7.10-7.35 (m, 3H), 7.55 (br s, 1H).

Step D: 3(R)-Amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, D-tartaric acid salt

3-Iodo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (1.79 Kg, 6.24 mol) was slurried in 6.2 L of methanol and the slurry charged into an autoclave. Condensed ammonia (1.55 L) was added and the autoclave closed, with stirring, and heated to 100°C over 1 hour. Heating at 100°C was continued for 2 hours then the autoclave was allowed to cool to room temperature over 1 hour, during which time the internal pressure was 150-155 psi. The reaction mixture was transferred to a polyethylene jug and the autoclave rinsed with 2x8 L of methanol. The washings were concentrated under vacuum at 30°C then combined with the reaction mixture and concentrated to near dryness under vacuum at 30°C. The resulting residue was dissolved in 4 L of ethyl acetate then concentrated to dryness under vacuum at 30°C.

Sodium chloride (712 g) was dissolved in 2 L of water and 1.0 Kg of sodium carbonate was dissolved in 6 L of water. Two liters of the sodium carbonate solution was added to the concentrated residue and the resulting slurry transferred to an extraction flask. Another 2 L portion of the sodium carbonate solution was added to the residue flask and the solution transferred to the extraction flask. The remaining sodium carbonate solution was used in the same way. The sodium chloride solution was added to the sodium carbonate/aminolactam emulsion and the resulting mixture stirred for 10 minutes then extracted with four 6 L portions of methylene chloride. The combined methylene chloride layers were concentrated to dryness; the residue was treated with 2 L of 200 proof ethanol and the resulting slurry concentrated to dryness under vacuum to give 1.171 Kg of crude product.

The crude product was slurried in 8 L of ethanol and treated with 900 g of D-tartaric acid in one portion. Water (7 L) was added and

the mixture heated to 77°C, then additional ethanol (45 L) was added and heating continued. The solution was cooled to 43°C and treated with the seed slurry. (The seed slurry was prepared by the route described above starting with 10.50 g of crude product and 9.1 g of D-tartaric acid.) The solution was aged at room temperature for 48 hours. The slurry formed was removed by filtration and the wet cake washed with 1.8 L of ethanol. The resulting filter cake was suction dried with nitrogen bleeding for 20 hours, then transferred into a drying tray and dried under vacuum for 24 hours to give 354 g (1.085 mol, 17.4%) of the product. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.13 (m, 1H), 2.51 (m, 2H), 2.73 (m, 2H), 3.68 (t, 6Hz, 1H), 3.98 (s, 2H), 7.05 (d, 8Hz, 1H), 7.16 (t, 8Hz, 1H), 7.30 (m, 2H), 7.6 (br s, 5H), 10.26 (br s, 1H).

Step E: 3(R)-Amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one

A solution of 229.23 g (0.700 mol) of 3(R)-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, D-tartrate in 4.1 L of water was treated with 194 g (1.40 mol) of potassium carbonate. Subsequent portions of 100 g and 135 g of potassium carbonate were added until the pH was 10.5. The mixture was extracted with four 4 L portions of methylene chloride which were then combined and dried over magnesium sulfate. The aqueous layer was treated with 1.4 Kg of sodium chloride and reextracted with four 4 L portions of methylene chloride which were then combined and dried over magnesium sulfate. The two 16 L batches of extracts were combined, filtered and concentrated to dryness under vacuum to give 115.5 g of product which contained 1.6% of an impurity identified as 7-iodo-3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one.

A solution of 107.02 g (0.607 mol) of the intermediate obtained above in 1.712 L of ethanol was hydrogenated at room temperature and 40 psi over 4.00 g of 10% palladium on carbon for 4 hours. The catalyst was removed by filtration through solkaflok and the filtrate concentrated to dryness under vacuum to give 101.08 g (0.574 mol, 94.4%) of product.

Step F: 2-Benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide

A solution of 3.18 g (18.0 mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one in 15 mL of methylene chloride was treated with 5.02 g (21.2 mmol; 1.2 eq) of N-carbobenzyloxy-2-methylalanine and 2.5 mL of triethylamine (1.82 g, 17.9 mmol, a eq.). The reaction flask was immersed in an ambient temperature water bath then 12.17 g (23.4 mmol, 1.3 eq) g of benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate was added all at once and the mixture stirred at room temperature for 2 hours. The reaction mixture was added to 50 mL of ethyl acetate and washed three times with 5% aqueous citric acid, twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride. The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. The residue was purified by preparative medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (4:1), to afford 7.42 g (18.76 mmol) of the product as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 3H), 1.52 (s, 3H), 1.82 (m, 1H), 2.50-3.00 (m, 3H), 4.45 (m, 1H), 5.05 (s, 2H), 5.37 (s, 1H), 6.80-7.40 (m, 10H), 8.65 (s, 1H). FAB-MS: calculated for $C_{22}H_{25}N_3O_4$ 395; found 396 (M+H,100%).

Step G: 4-Bromobenzyl-t-butyldiphenylsilyl ether

To a solution of 28.2 g (0.150 mol) of 4-bromobenzylalcohol in 470 mL of dry dimethylformamide under nitrogen atmosphere was added 31.4 mL (0.225 mol) of triethylamine. The reaction mixture was cooled to 0°C and 43 mL (0.17 mol) of t-butylchlorodiphenylsilane was added dropwise by addition funnel. The reaction mixture was stirred at ambient temperature overnight then poured into a separatory funnel containing 1L of diethyl ether and 500 mL of water. To this mixture was added 125 mL of 2N aqueous hydrochloric acid. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 350 mL). The organic extracts were combined, washed with water (2 x 250 mL) and dried over magnesium sulfate. The solids were removed by

filtration and the solvent removed under vacuum to give an oil which crystallized on standing. The flask containing the crude product was placed in the freezer overnight then triturated with a minimal amount of methanol and filtered. The solid was air dried for several hours then dried under vaccuum overnight to afford 59.5 g (93%) of product as an off-white solid (mp 44-47°C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (s, 9H), 4.76 (s, 2H), 7.25 (d, 8Hz, 2H), 7.45 (m, 8H), 7.75 (m, 4H). FAB-MS: calculated for $C_{23}H_{25}BrOSi$ 424; found 425 (M+H, 7%).

Step H: 4-(t-Butyldiphenylsiloxymethyl)phenylboronic acid

To a solution of 20 g (47 mmol) of 4-bromobenzyl-t-butyldiphenyl silyl ether in 200 mL of dry tetrahydrofuran under a nitrogen atmosphere at -78°C was added dropwise by syringe 19.74 mL (49.35 mmol) of a 2.5M solution of n-butyl lithium in hexanes over twenty minutes. The resulting mixture was stirred for thirty minutes, then 11.6 mL (50.3 mmol) of triisopropyl borate was added by syringe. The reaction mixture was stirred at -78°C for thirty minutes then slowly warmed to room temperature and stirred for an additional two hours. The reaction mixture was then quenched by the addition of 750 mL of water containing 100 mL of concentrated hydrochloric acid and 500 mL of diethyl ether. The mixture was strirred for one hour and then the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 400 mL). The combined ether extracts were washed with saturated aqueous sodium chloride (4 x 100 mL), dried over magnesium sulfate and filtered. The solvent was removed under vacuum to give an oil which was crystallized by dissolving in hexanes and evaporation of the solvent under vacuum to afford 15.6 g (85%) of product as a white solid (mp 171-174°C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (s, 9H), 4.86 (s, 2H), 7.40 (m, 6H), 7.58 (d, 8Hz, 2H), 7.70 (m, 4H), 8.22 (d, 8Hz, 2H). FAB-MS: calculated for $C_{23}H_{27}BrO_3Si$ 390; found 372 (M-H_2O).

Step I: N-(t-Butoxycarbonyl)-2-bromobenzylamine

To a slurry of 8.88 g (39.9 mmol) of 2-bromobenzylamine hydrochloride in 100 mL of dry methylene chloride under a nitrogen

atmosphere was added by syringe 12.24 mL (87.80 mmol) of triethylamine. The resulting solution was stirred at 0°C for five minutes then treated with 9.6 g (44 mmol) of di-t-butyldicarbonate. The reaction was stirred at room temperature for two hours then diluted with 350 mL of methylene chloride. The solution was washed with water (2 x 150 mL), saturated aqueous ammonium chloride (150 mL), saturated aqueous sodium bicarbonate (4 x 150mL) and saturated aqueous sodium chloride (150 mL), dried over sodium sulfate and filtered. The solvent was removed under vacuum to give an oil which was crystallized by dissolving in hot hexanes, filtering and cooling the solution. The product was filtered and dried under vacuum to afford 8.66 g (90%) of the product as a white solid (mp 51-53°C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 4.37 (d, 5Hz, 2H), 5.00 (s, 1H), 7.10 (m, 1H), 7.25 (m, 1H), 7.35 (m, 1H), 7.40 (d, 6Hz, 1H). FAB-MS: calculated for $C_{12}H_{16}BrNO_2$ 285; found 286 (M+H).

Step J: 2'-[(t-Butoxycarbonylamino)methyl]-4-[(t-butyldiphenylsiloxy)methyl]-1,1'-biphenyl

To a solution of 3.2 g (8.2 mmol) of 4-(t-butyldiphenylsilyoxymethyl)phenylboronic acid in 64 mL of benzene was added 2.2 mL of water, 6.4 mL of 5N aqueous sodium hydroxide, and 8.3 mL of isopropanol. To this mixture was added 180 mg (0.16 mmol) of tetrakis(triphenylphosphine) palladium and 2.20 g (7.81 mmol) of N-(t-butoxycarbonyl)-2-bromobenzylamine. The resulting mixture was heated under nitrogen at reflux for 2 hours then cooled to room temperature. The reaction mixture was diluted with 100 mL of water, transferred to a separatory funnel and extracted with ether (3 x 150 mL). The combined ether extracts were washed with saturated aqueous sodium bicarbonate (100 mL) and saturated aqueous sodium chloride (100 mL), dried over magnesium sulfate and filtered. The solvent was removed under vacuum to give a crude product which was purified by column chromatography on silica gel eluting with hexanes/ethyl acetate (9:1) to afford 4.31 g (100%) of the product as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.41 (s, 9H), 4.27 (d, 6Hz, 2H), 4.45 (m, 1H), 4.81 (s, 2H),

7.20-7.49 (m, 14H), 8.72 (m, 4H). FAB-MS: calculated for $C_{35}H_{41}NO_3Si$ 551; found 552 (M+H).

Step K: 2'-[(t-Butoxycarbonylamino)methyl]-1,1'-biphenyl-4-methanol

To a solution of 3.85 g (7.00 mmol) of 2'-[(t-butoxycarbonylamino)methyl]-4-[(t-butyldiphenylsiloxy)methyl]-1,1'-biphenyl in 25 mL of dry tetrahydrofuran under a nitrogen atmosphere was added by syringe 10.5 mL (0.530 mmol) of a 1.0M solution of tetra-n-butylammonium fluoride in tetrahydrofuran. The reaction mixture was stirred for two hours then diluted with 700 mL of diethyl ether. The mixture was washed with water (3 x 150 mL), saturated aqueous sodium bicarbonate (50 mL), saturated aqueous sodium chloride (50 mL), then dried over magnesium sulfate and filtered. The solvent was removed under vacuum to give an oil which was purified by column chromatography on silica gel eluting with hexanes/ethyl acetate (55:45) to afford 2.02 g (92%) of the product as a white solid (mp 89-93°C). ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.50 (s, 2H), 4.20 (s, 2H), 4.70 (s, 2H), 7.18-7.45 (m, 8H). FAB-MS: calculated for $C_{19}H_{23}NO_3$ 313; found 314 (M+H).

Step L: 2'-[(t-Butoxycarbonylamino)methyl]-1,1'-biphenyl-4-methanol, methanesulfonate ester

To solution of 53 mg (0.17 mmol) of 2'-[(t-butoxycarbonylamino)methyl]-1,1'-biphenyl-4-methanol in 1 mL of dry methylene chloride under nitrogen atmosphere at 0°C was added by syringe 0.035 mL (0.25 mmol) of triethylamine followed by 0.016 mL (0.20mmol) of methanesulfonyl chloride. The reaction mixture was stirred for 2 hours at 0°C then diluted with 75 mL of methylene chloride, washed with water, saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, dried over sodium sulfate and filtered. The solvent was removed under vacuum to give 61 mg (97%) of the product as a white solid which was used in the next step without further purification. ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 2.95 (s, 3H),

4.20 (d, 5Hz, 2H), 4.65 (s, 1H), 5.25 (s, 2H), 7.18-7.50 (m, 8H). FAB-MS: calculated for $C_{20}H_{25}NO_5S$ 391; found 392 (M+H).

Step M: 2-Benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[(t-butoxycarbonylamino)methyl][1,1'-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(R)-yl]propanamide

To a solution of 819 mg (2.07 mmol) of 2-benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide in 7.0 mL of dry dimethylformamide under nitrogen at 0°C was added 83 mg (2.1 mmol) of 60% sodium hydride/oil dispersion. After stirring for 15 minutes, a solution of 810 mg (2.1 mmol) of 2'-[(t-butoxycarbonylamino)methyl]-1,1'-biphenyl-4-methanol, methanesulfonate ester in 2.0 mL of dimethylformamide was added by cannula. The flask which originally contained the methanesulfonate ester was rinsed with 1.0 mL of dimethylformamide which was added to the reaction mixture. After stirring at 0°C for 15 minutes, the reaction mixture was diluted with 400 mL of ethyl acetate and 50% saturated ammonium chloride. The mixture was transferred to a separatory funnel and the aqueous layer was separated. The organic layer was washed with 100 mL of saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (55:45) to afford 1.2 g (84%) of the product as a white foam. ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.48 (s, 3H), 1.52 (s, 3H), 1.78 (s, 1H), 2.35-2.70 (m, 3H), 4.18 (d, 6Hz, 2H), 4.38-4.62 (m, 2H), 4.82 (d, 16Hz, 1H), 5.05 (s, 2H), 5.25 (d, 16Hz, 1H), 5.32 (s, 1H), 7.08 (d, 6Hz, 1H), 7.12-7.43 (m, 18H). FAB-MS: calculated for $C_{41}H_{46}N_4O_6$ 690; found 691(M+H).

Step N: 2-Benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(aminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(R)-yl]propanamide, hydrochloride

To a solution of 9.83 g (0.55 mmol) of 2-benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[(t-butoxycarbonylamino)methyl][1,1'-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(R)-yl]propanamide in 170 mL of methanol was added 120 mL of 9N aqueous hydrochloric acid. Periodically 10 mL portions of methanol were added to the reaction mixture to dissolve precipitates which form during the reaction (50 mL total). The reaction mixture was stirred overnight at room temperature then the solvent was removed under vacuum. The resulting oil was dissolved in methanol and the solvent was removed under vacuum to afford 8.57 g (96%) of the title compound as an off-white foam. ^{1}H NMR (200 MHz, CD_3OD): δ 1.40 (s, 6H), 1.90 (m, 1H), 2.20-2.65 (m, 3H), 4.02 (s, 2H), 4.32 (m, 1H), 4.96 (d, 16Hz, 1H), 5.00 (s, 2H), 5.25(d, 16Hz, 1H), 7.08-7.65 (m, 17H). FAB-MS: calculated for $C_{36}H_{38}N_4O_4$ 590; found 591(M+H, 100%).

Step O: 2-Benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]-propanamide

To a solution of 8.57 g (13.7 mmol) of 2-benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(aminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-benzazepin-3(R)-yl]-propanamide, hydrochloride in 75 mL of dry methylene chloride under nitrogen atmosphere was added 2.28 mL (16.4 mmol) of triethylamine followed by 0.89 mL (15 mmol) of methyl isocyanate. After stirring at room temperature for 45 minutes the solvent was removed under vacuum. The resulting material was dissolved in methylene chloride and purified by flash column chromatography on silica gel eluting with ethyl acetate/methanol (96:4) to afford 7.73 g (87%) of product as a white foam. ^{1}H NMR (200 MHz, CD_3OD): δ 1.39 (s, 6H), 1.82 (m, 1H), 2.15-2.60 (m, 3H), 2.63 (s, 3H), 4.13 (s, 2H), 4.36 (m, 1H), 4.86 (d, 15Hz, 1H), 4.85 (s, 2H), 5.32 (d, 15Hz, 1H), 7.08-7.43 (m, 17H). FAB-MS: calculated for $C_{38}H_{41}N_5O_5$ 647; found 648(M+H, 80%).

Step P: 2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide, hydrochloride

To a solution of 5.00 g (7.72 mmol) of 2-benzyloxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-1-[[2'-[[[(methylamino)carbonyl]amino]methyl][1,1'-biphenyl]-4-yl]methyl]-2-oxo-1*H*-benzazepin-3(R)-yl]propanamide in 100 mL of dry methanol was added 0.50 g (0.1 equiv. by weight) of palladium hydroxide. The mixture was stirred under hydrogen atmosphere for 2 hours. The mixture was filtered through Celite. The filter pad was washed with 50 mL of methanol. The filtrate was combined and the solvent was removed under vacuum. The resulting oil was dissolved in 50 mL of methanol and treated with 17 mL (8.5 mmol) of a 0.499N aqueous hydrochloric acid solution. The solvent was removed under vacuum to give a solid which was crystallized by refluxing in 480 mL of acetonitrile/ethanol (7:1). The mixture was cooled to room temperature with gentle stirring. After 3 hours the solids were filtered and washed with 80 mL of ice cold acetonitrile/ethanol (7:1) and then air dried for 3 hours. The resulting solid was dissolved in 40 mL of water, filtered and lyophilized overnight to afford 3.78 g (89%) of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.55 (s, 3H), 1.64 (s, 3H), 2.28 (m, 2H), 2.62 (m, 2H), 2.67 (s, 3H), 4.16 (dd; 16, 14Hz; 2H), 4.39 (dd; 12, 8Hz; 1H), 5.00 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 7.14 (d, 7Hz, 1H), 7.20-7.41 (m, 11H). FAB-MS: calculated for $C_{30}H_{35}N_5O_3$ 513; found 514 (M+H, 100%).

EXAMPLE 4 (METHOD 1)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

Step A: 1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdine]hydrochloride

To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperdine] (prepared as described by H. Ong, et al., J. Med. Chem., 23, 981-986 (1983)) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%).
^{1}H NMR ($CDCl_3$, 200MHz) δ 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

Step B: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methyl-propanamide

To 0.35g (1.15 mmol) of (2R)-2-[(1,1-dimethylethoxy)-carbonyl]amino-3-[2-(phenylmethyloxy)ethyl]-1-propanoic acid in 13 mL of dichloromethane was added 1,2-dihydro-1-methanesulfonylspiro-[3H-

indole-3,4'-piperdine] hydrochloride (0.325 g; 1.07 mmol), 0.18 mL (1.63 mmol) of N-methylmorpholine, 0.159 g (1.18 mmol) of 1-hydroxybenztriazole(HOBT) and stirred for 15 min. EDC (0.31 g; 1.62 mol) was added and stirring was continued for 1h. An additional 60 µL of N-methylmorpholine was added and stirred for 45 min. The reaction mixture was poured into 5 mL of water and the organic layer was separated. The organic layer was washed with 5 mL of 0.5N aqueous hydrochloric acid and 5 mL of saturated aqueous sodium bicarbonate solution. The combined organics were dried over anhydrous magnesium sulfate, and concentrated to yield 0.627 g of the product as a yellow foam which was used without purification.

To a 0.627 g (1.07 mmol) of the above product in 5 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid and stirred at RT for 75 min. An additional 1.00 mL of trifluoroacetic acid was added and stirred for 10 min. The reaction mixture was concentrated, diluted with 5.0 mL of dichloromethane and carefully basified by pouring into 10 mL of 10% aqueous sodium carbonate solution. The organic layer was separated and the aqueous layer was further extracted with 2X15 mL of dichloromethane. The combined organics were washed with 5 mL of water, dried over potassium carbonate, filtered and concentrated to give the 0.486 g of the amine as a light yellow foam which was used without purification.

To 0.486 g (1.01 mmol) of the amine and 10 mL of dichloromethane was added 0.26g (1.28 mmol) of 2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanoic acid, 0.173 g (1.28 mmol) of 1-hydroxybenztriazole (HOBT) and EDC (0.245 g; 1.28 mol) and stirried at RT overnight. The reaction mixture was poured into 5.0 mL of water and the organic layer was separated. The aqueous layer was back extracted with 5 mL of dichloromethane. The combined organics were washed with 5.0 mL of 0.5N aqueous hydrochloric acid, 5 mL of saturated aqueous sodium bicarbonate solution dried over anhydrous magnesium sulfate, and concentrated to yield 0.751 g of the crude product as a yellow foam. A solution of this crude product in dichloromethane was chromatographed on 25 g of silica gel and eluted

first with hexanes/acetone/dichloromethane (70/25/5) and then with hexanes/acetone/dichloromethane (65/30/5). This gave 0.63 g of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To 0.637 g (0.101 mmol) of the intermediate from Step B in 5 mL of dichloromethane was added 2.5 mL of trifluoroacetic acid and stirred at RT for 30 min. The reaction mixture was concentrated to an oil, taken up in 10 mL of ethyl acetate and washed with 8 mL of 10% aqueous sodium carbonate solution. The aqueous layer was further extracted with 5 mL of ethyl acetate. The combined organics were washed with 10 mL of water, dried over magnesium sulfate, filtered and concentrated to give the 0.512 g of the free base as a white foam.

To 0.512 g of the free base in 5 mL of ethyl acetate at 0°C was added 0.2 mL of saturated hydrochloric acid in ethyl acetate and stirred for 1.5 h. The white precipitate was filtered under nitrogen, washed with ether, and dried to give 0.50 g of the title compound as a white solid ^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 4 (METHOD 2)

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl) carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide

Step A: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethoxy)ethyl]-1-propanoic acid allyl ester

Prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]-amino-3-(phenylmethyloxy)ethyl-propanoic acid and allyl alcohol by carrying out the coupling reaction in CH_2Cl_2 in the presence of EDC and DMAP. ^1H NMR (400MHz, $CDCl_3$) δ 7.25 (s, 5H), 5.8 (m, 1H), 5.2 (dd, 2H), 5.0 (bs, 1H), 4.7 (m, 1H), 4.6 (m, 2H), 4.4 (dd, 2H), 3.9 (dd, 1H), 3.6 (dd, 1H), 1.45 (d, 6H), 1.39 (s, 9H).

Step B: (2R)-[[[-2-(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxoethyl]amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid

To a stirred solution of the crude intermediate obtained in Step A (6.7 g, 15.9 mmol), tetrakis (triphenylphosphine)-palladium (1.8 g, 0.1 eq) and, triphenyl phosphine (1.25 g, 0.3 eq) was added a solution of potassium-2-ethyl hexanoate (35 mL, 0.5M solution in EtOAc). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1h and then diluted with ether (100 mL) and poured into ice-water. The organic layer was seperated and the aqueous fraction was acidified with citric acid (20%), then extracted with EtOAc. The EtOAc extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to give the title compound as a solid. ^1H NMR (400Hz, CD_3OD) δ 7.3 (s, 5H), 4.7 (m, 1H), 4.5 (s, 2H), 4.0 (m, 1H), 3.6 (m, 1H), 1.4 (d, 6H), 1.3 (s, 9H).

Step C: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-[(1,1-dimethyl-ethoxy)carbonyl]amino-2-methyl-propanamide

To a solution of 1.0 g (3.44 mmol) of 1-methanesulfonyl-spiro[indoline-3,4'-piperidine] hydrochloride, 1.44 g (3.78 mmol) of (2R)-[[-2-(1,1-dimethylethoxy)carbonyl)amino]-2,2-dimethyl-1-oxo-ethyl]-amino-2-(phenylmethyloxy)ethyl)-1-propanoic acid, N-methyl morpholine (0.58 mL; 5.20 mmol), and 1-hydroxybenztriazole (HOBT) (0.58 g; 3.78 mmol), in 50 mL of dichloromethane was added EDC (1.03 g; 5.20 mmol) and stirred at RT for 16h. The reaction mixture was diluted with an additional 50 mL of dichloromethane and washed with aqueous sodium bicarbonate solution (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography (50 g silica gel) of the crude oily residue gave 2.148 g (90%) of the desired material as a colorless foam. ^{1}H NMR ($CDCl_3$, 400MHz) Compound exists as a 3:2 mixture of rotamers δ 7.40-7.10 (m, 6H), 7.06 (d, 1/3H), 7.02 (t, 1/3H), 6.90 (t, 1/3H), 6.55 (d, 1/3H), 5.15 (m, 1H), 4.95 (bs, 1H), 4.63 (bd, 1/3H), 4.57-4.40 (m, 2 2/3 H), 4.10 (bd, 1/3H), 4.00 (bd, 1/3H), 3.82 (t, 1H), 3.78-3.62 (m, 2H), 3.60-3.50 (m, 1H), 3.04 (q, 1H), 2.87 (s, 1H), 2.86 (s, 2H), 2.80-2.60 (m, 1H), 1.90 (bs, 1H), 2.85-2.75 (m, 1H), 1.82-1.60 (m, 3H), 1.55-1.45 (m, 1H), 1.45 (s, 4H), 1.42 (s, 2H), 1.39 (s, 9H).

Step D: N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide hydrochloride

To a solution of 2.148 g (3.41 mmol) of the intermediate from Step C in 10 mL of dichloromethane was added 5 mL of trifluoroacetic acid and stirred for 1h. The reaction mixture was concentrated and basified with 100 mL of 5% aqueous sodium carbonate solution and extracted with dichloromethane (3X50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous potassium carbonate, filtered, and concentrated to yield a colorless foam.

To a solution of the foam in 25 mL of ethyl acetate at 0°C was added 4 mL of 1M solution of hydrochloric acid in ethyl acetate. The precipitate was filtered and washed first with ethyl acetate and then with ethyl acetate-ether (1:1), dried to yield 1.79 g (93%) of the title compound as a colorless solid. ^{1}H NMR (400MHz, CD_3OD) Compound exists as 3:2 mixture of rotamers. δ 7.40-7.28 (m, 4H), 7.25-7.17 (m, 2H), 7.08 (t, 1/3H), 7.00 (t, 1/3H), 6.80 (d, 1/3H), 5.16 (ddd, 1H), 4.60-4.42 (m, 3H), 4.05 (t, 1H), 3.90 (bs, 2H), 3.83-3.70 (m, 2H), 3.30-3.15 (m, 1H0, 2.97 (s, 1H), 2.95 (s, 2H), 2.90-2.78 (m, 1H), 1.96 (t, 1/3H), 1.85-1.65 (m, 4H), 1.63 (s, 2H), 1.60 (s, 4H).

EXAMPLE 5

N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperdin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methyl-propanamide mesylate

This compound was prepared by the treating the free base obtained in Example 4, Step D, with methane sulfonic acid. The title compound was obtained by recrystallizing it from ethyl acetate-ethanol-water. m.p. = 166°-168°C.

EXAMPLE 6

N-[1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-[3-phenylpropyl]-2-amino-2-methyl-propanamide hydrochloride

Step A: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-[(1,1-dimethylethoxy)carbonyl]amino-2-methylpropanamide

The title compound was prepared from (2R)-2-[(1,1-dimethylethoxy)carbonyl]amino-4-phenyl-1-butanoic acid and 1,2-dihydro-1-methylsulfonylspiro[3H-indole-3,4'-piperidine] hydro-chloride by using the coupling method as described in Example 4, Step B. The crude product was purified on silica gel using 5% Acetone in CH_2Cl_2.

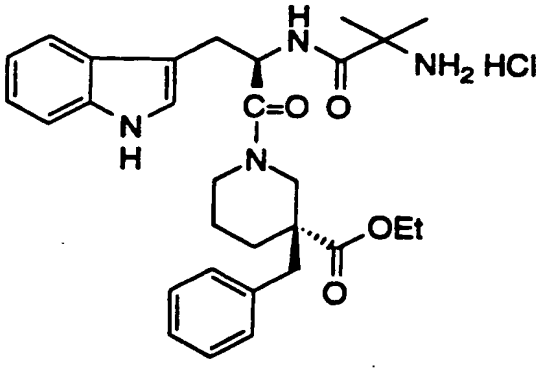
^{1}H NMR (400MHz, $CDCl_3$) δ 7.2 (m, 9H), 4.9 (m, 1H), 4.5 (m, 1H), 3.8 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 2H), 2.3 (s, 2H), 2.0 (m, 2H), 1.7 (m, 4H), 1.5 (s, 6H), 1.4 (s, 9H).

Step B: N-1(R)-[1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methylpropanamide hydrochloride

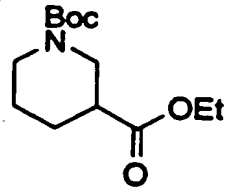
Prepared from the intermediate obtained in step A using the deprotection method as described in Example 4, Step C.

^{1}H NMR (400MHz, CD_3OD) δ 7.3 (m, 9H), 4.5 (m, 1H), 3.9 (m, 2H), 3.5 (m, 2H), 3.2 (m, 2H), 2.9 (s, 3H), 2.7 (m, 4H), 2.0 (m, 4H), 1.6 (s, 6H).

EXAMPLE 7



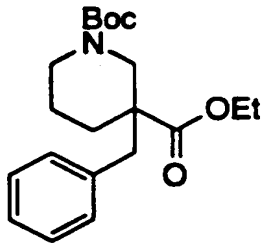
Step A:



To a stirred solution of ethyl nipecotate (15 g, 95.4 mmol) and DMAP (0.05 eq.) in dichloromethane at 0°C was added dropwise by an addition funnel di-tert-butyl dicarbonate (21.8 g, 100 mmol) in dichloromethane (200 mL). The mixture was stirred for 2-3 hours. The

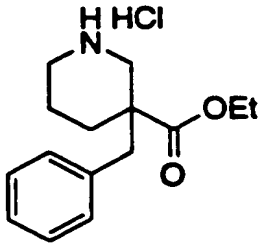
solution was washed with 3 N HCl and saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated to give the desired product (18.7 g, 88%).

Step B:



To a stirred solution of ethyl N-t-Boc nipecotate (7 g, 26.90 mmol) in THF (100 mL) at -78°C under argon was added LHMDS (28 mL, 28 mmol) over a 10 minute period. The solution was allowed to stir an additional 30 minutes at -78°C; then benzyl bromide (4.8 g, 28 mmol) was added slowly to the solution. The reaction mixture was stirred overnight and allowed to warm to room temperature. The material was concentrated, then diluted with water, and extracted using ethyl acetate (2 x 200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by silica gel flash column chromatography, eluting with 20% ethyl acetate in hexane, provided the title compound. (8.32 g, 88%). FAB-MS calc. for $C_{20}H_{29}NO_4$: 347; Found 348 (M+H)

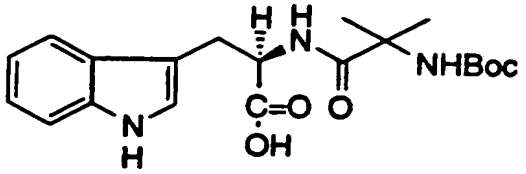
Step C-1:



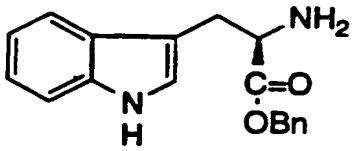
A solution of the intermediate from Step B (8 g, 23.02 mmol) in ethyl acetate (80 mL) was cooled to 0°C. While stirring,

hydrogen chloride gas was bubbled into the mixture until saturation occurred. The reaction was stirred for 40 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford the product (6.53 g, 99%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.25-7.19 (m, 3 H), 7.04-7.01 (m, 2 H), 5.35 (v. br. s, 2 H), 4.22-4.10 (m, 2 H), 3.44 (d, J = 13 Hz, 1 H), 3.21 (br. d, J = 12.7 Hz, 1 H), 2.95 (d, J = 13.5 Hz, 1 H), 2.76-2.68 (m, 3 H), 2.22 (br. d, J = 13 Hz, 1 H), 1.73-1.71 (m, 1 H), 1.61-1.48 (m, 2 H), 1.18 (t, J = 7 Hz, 3 H). FAB-MS calc. for $C_{15}H_{21}NO_2$: 247; Found 248 (M+H)

Step C-2



Step C-2A:

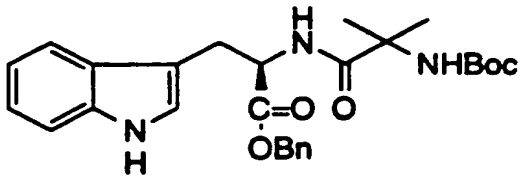


To a solution of the commercially available N-t-BOC-D-tryptophan (25.0 g, 82.2 mmol), benzyl alcohol (10.2 mL, 98.6 mmol), and DMAP (100 mg) in dichloromethane (200 mL) at 0°C, was added EDC (17.4 g, 90.4 mmol) in several portions over a one hour period. The reaction mixture was stirred at room temperature for six hours and was poured into water (200 mL), and the organic layer was separated. The organic solution was washed with a mixture of brine and 3 N hydrochloric acid, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which solidified upon standing.

To a solution of this oil in 30 mL of dichloromethane was added 20 mL of TFA and stirred for 1h. The reaction mixture was

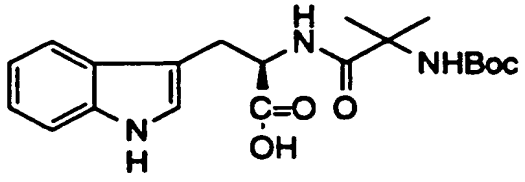
concentrated, neutralized carefully with saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane (2X100 mL). The combined organic solution was washed with brine (100 mL), passed through a short column of silica gel eluting with 5-10% methanol in dichloromethane to give 23.2 g of the amine as an oil after evaporation.

Step C-2B:



To a solution of the product from Step C-2A, HOBT (10.6 g, 78.8 mmol) and N-BOC-α-methyl alanine (19g, 94.5 mmol) in 200 mL of dichloromethane, was added EDC (19.5 g, 0.102 mol) in several portions at 0°C. After 5 minutes, the clear reaction mixture became milky. After stirring at room temperature overnight, the reaction mixture was poured into 200 mL of water and the organic layer was separated. The organic solution was washed with brine, and with a brine and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which was purified by flash chromatography eluting with 10-40% ethyl acetate in hexane to give the desired material (28.7 g). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.48 (br.s, 1H), 7.54 (br.d, 1H), 7.38-7.23 (m, 3H), 7.19 (br.d, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (br.s, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

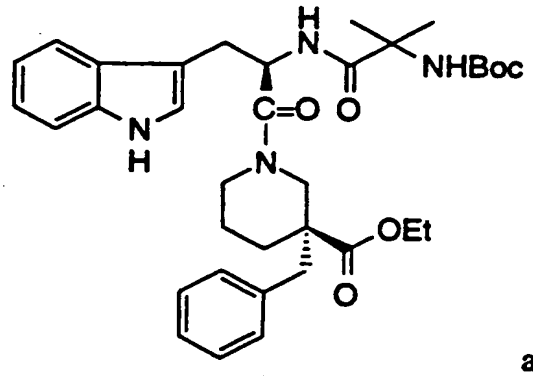
Step C-2C:



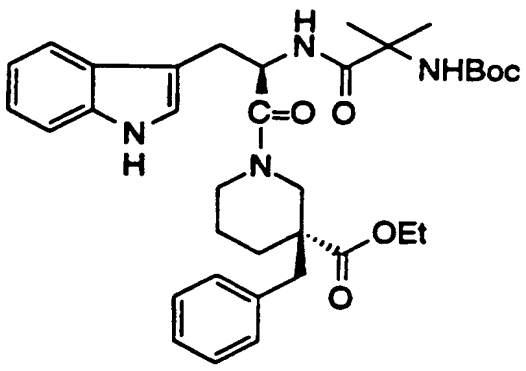
A solution of the material from Step C-2B (28.7g) in 200 mL of ethanol was stirred at RT under a H_2 balloon for 20 minutes in the

presence of 10% palladium on carbon (2 g). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a slightly pink foam (23.3 g).
^{1}H NMR (CD_3OD, 400 MHz) δ 7.56 (d, J=8 Hz, 1 H), 7.31 (dd, J=1, 8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (dt, J=1, 7 Hz, 1 H), 6.98 (dt, J=1, 7 Hz, 1 H), 4.69 (t, J=6 Hz, 1 H), 3.34-3.23 (m, 2 H), 1.35 (s, 3 H), 1.34 (s, 9 H), 1.29 (s, 3 H). FAB-MS calc. for $C_{20}H_{27}N_3O_5$: 389 ; Found 390 (M+H), 290 (M+H-100 (BOC))

Step D:

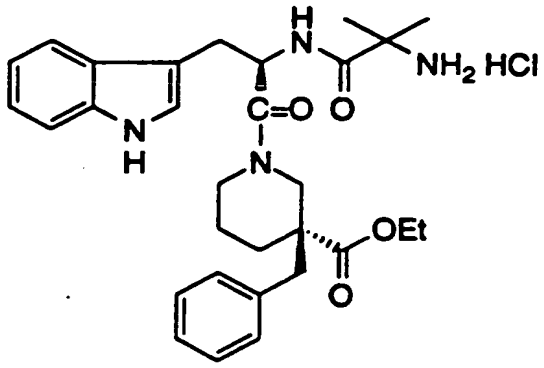


and



To a solution of the intermediate prepared in the previous step (1.2 g, 4.23 mmol), and the intermedate from Step C-2C (1 eq.), HOBT (1 eq.), and N-methyl morpholine (1 eq.) in dichloromethane cooled to 0°C was added EDC (1.5 eq.). The reaction mixture was stirred at 0°C overnight. The solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate; then filtered and concentrated. Purification by MPLC eluting with 40% ethyl acetate in hexane provided two enantiomerically pure compounds. The compound which came out first from the column was designated as d1 (1.14g), which has an R-absolute stereochemistry at the 3-position of the nipecotate; and the compound which came out of the column second was designated as d2 (1.08 g), which has an S-absolute stereochemistry (see Example 2 for assignment) at the 3-position of the nipecotate.
d1 FAB-MS calc. for $C_{35}H_{46}N_4O_6$: 618; Found 619 (M+H)
d2 FAB-MS calc. for $C_{35}H_{46}N_4O_6$: 618; Found 619 (M+H)

Step E:



Prepared by the procedure described in Step C-1 of Example 8 from 1 g of the d2 intermediates from the Step D of Example 8 in ethyl acetate (20 mL) by bubbling HCl at 0°C until saturated and then evaporated after 30 minutes to give the title compound (878 mg, 93%). FAB-MS calc. for $C_{30}H_{38}N_4O_4$: 518; Found 519 (M+H) ^1H NMR (CD_3OD, 400MHz) compound exists in two rotamers in approximately a 5/3 ratio that slowly interconvert relative to the NMR time scale δ 7.60 (d, J = 7.9 Hz, 5/8 H), 7.55 (d, J = 7.9 Hz, 3/8 H), 7.34-6.93 (m, 9H), 5.36 (dd, J = 5.2Hz, 9.7 Hz, 3/8 H), 5.31 (dd, J = 6.7 Hz, 8.8 Hz, 5/8 H), 4.23 (br. d, J = 13.7 Hz, 3/8 H), 4.10-4.00 (m, 6/8 H), 4.04-3.98 (m, 3/8 H), 3.96-3.82 (m, 10/8 H), 3.80 (br. d, J = 13.5 Hz, 5/8 H), 3.36 (br. d, J = 13.3 Hz, 5/8 H), 3.29-3.22, 3.17-3.10, (2m, 2H), 3.20 (br. d, J = 14.5 Hz, 3/8 H), 3.10-2.96 (m, 5/8 H), 2.90 (s, 6/8 H), 2.60 (d, J = 13.4 Hz, 5/8), 2.41 (d, J = 13.4 Hz, 5/8 H), 2.19-2.12, 1.82-1.70, 1.68-1.60, 1.50-1.40, 1.34-1.25, 1.05-0.95 (6m, 4 H),1.55 (s, 9/8 H), 1.50 (s, 15/8 H), 1.09 (t, J = 7.1 Hz, 3 H).

EXAMPLE 8

Study of N-[1(R)-[(1,2-Dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide in Congestive Heart Failure.

The effect of administration of a growth hormone secretagogue may be examined in a canine model of congestive heart failure as follows. After table training for several weeks, the subject dogs are anesthetized and by means of a left thoracotomy, pacing wires are placed on the left atrial appendage and right ventricle, tygon catheters are inserted into the descending aorta and the right and left atria, a solid state micromanometer is inserted in the left ventricle, a flow probe is placed around the ascending aorta and the coronary artery, and piezoelectric crystals are placed in the left ventricle. If desired, renal and iliac arterial flow probes may also be placed. The animals are permitted to recover for 14 days during which time basal measurements are obtained. Pacing of the right ventricle at approximately 240 beats/minute is initiated on day 14 after surgery. As demonstrated by hemodynamic data at baseline and at three weeks after pacing in a conscious dog, this model not only achieves significant left ventricular dysfunction (i.e. a decrease in left ventricular change in pressure over change in time and ejection fraction, increase in left ventricular end diastolic pressure and heart rate), but also demonstrates many of the signs of congestive heart failure seen in the clinic, including exercise intolerance, pulmonary edema, and ascites.

On day 14 after surgery, the subject animals are randomized (target five animals in each group). The compound N-[1(R)-[(1,2-dihydro-1-methane-sulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide or vehicle is administered beginning at the time of the initiation of pacing throughout the duration of the study. Cardiac function, peripheral hemodynamics, exercise performance and body weights are measured in the baseline study and weekly after initiation of pacing (three weeks total). Twenty-one days after initiation of pacing, the animals are

sacrificed and the relative effect of administration of the growth hormone secretagogue on ventricular modeling, left ventricular mass, and body weight is determined.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

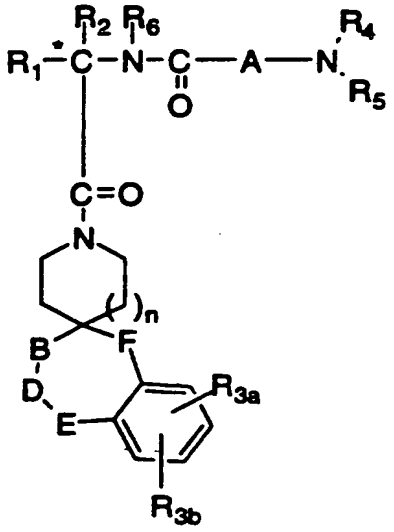
1. A method of treating congestive heart failure in a mammal which comprises the administration of a therapeutically effective amount of a growth hormone secretagogue.

2. The method of Claim 1 wherein the growth hormone secretagogue is an orally active growth hormone secretagogue.

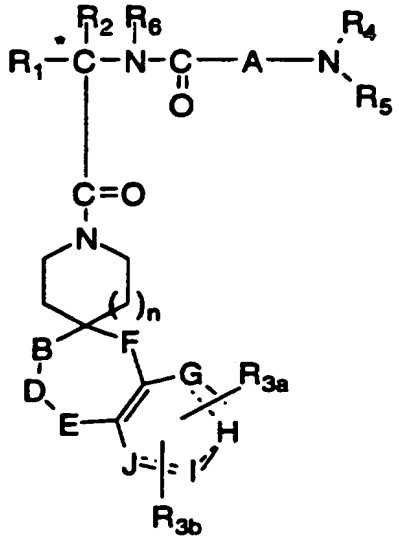
3. The method of Claim 2 wherein the growth hormone secretagogue is orally administered.

4. The method of Claim 1 wherein the mammal is a human.

5. The method of Claim 1 wherein the growth hormone secretagogue is selected from the group consisting of:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, OC(O), C(O)O, or $-CR_2=CR_2-$, or -C≡C-,

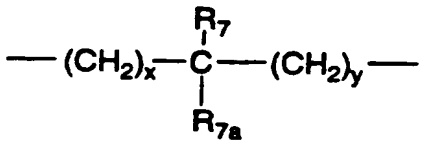
and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};
R_{2a} is hydrogen, or C_1-C_6 alkyl;

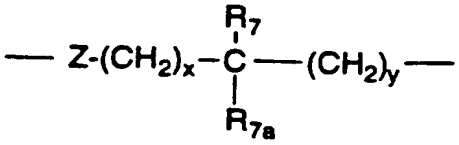
R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m$(C_1-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;
R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -$N=CR_{10}$- or -$CR_{10}=N$-, or B and D, or D and E taken together may be -$CR_8=CR_{10}$-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, (-CH_2)$_q$-aryl, -(CH_2)$_q$-$C(O)OR_2$, -(CH_2)$_q$-$C(O)O(CH_2)_q$-aryl, or -(CH_2)$_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R_9 is selected from the group consisting of:
-R_2, -(CH_2)$_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,

and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 $-OR_{2a}$, $-O(CH_2)_q$ aryl, 1 to 2 $-C(O)OR_{2a}$, 1 to 2 $-C(O)O(CH_2)_q$ aryl, 1 to 2 $-C(O)N(R_{2a})(R_{2a})$, 1 to 2 $-C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R_{2a}$, $-S(O)_mR_{2a}$, $-C(O)NHSO_2(CH_2)q$-aryl, $-SO_2NHC{\equiv}N$, $-SO_2NHC(O)R_{2a}$, $-SO_2NHC(O)(CH_2)_q$aryl, $-N(R_2)C(O)N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)N(R_{2a})(CH_2)_q$-aryl, $-N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)R_{2a}$, $-N(R_{2a})C(O)(CH_2)q$ aryl, $-OC(O)N(R_{2a})(R_{2a})$, $-OC(O)N(R_{2a})(CH_2)_q$ aryl, $-SO_2(CH_2)_qCONH$-$(CH_2)wNHC(O)R_{11}$, wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1, or 2;

q may optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring; and pharmaceutically acceptable salts and individual diastereomers thereof.

6. The method of Claim 1 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

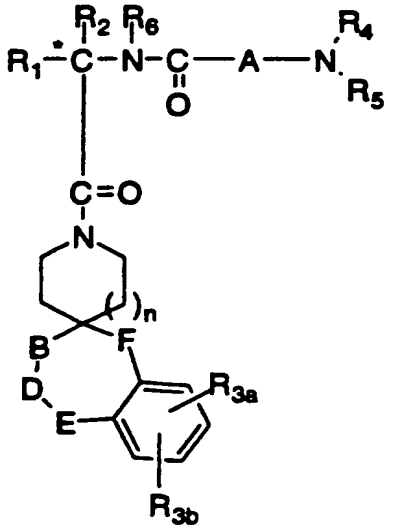
6. A method of treating congestive heart failure in a mammal which comprises administering a therapeutically effective amount of a growth hormone secretagogue in combination with an antihypertensive agent.

7. The method of Claim 6 wherein the antihypertensive agent is selected from: a diuretic, an angiotensin converting enzyme inhibitor, a calcium channel blocker, and a β-blocker.

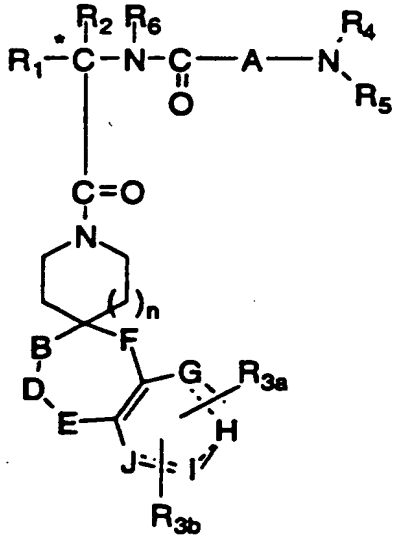
8. The method of Claim 6 wherein the mammal is a human.

9. The method of Claim 6 wherein the antihypertensive agent is selected from the group consisting of: A-69729, acetazolamide, alacepril, altizide, amiloride, aminophylline, amrinone, azosemide, atenolol, atriopeptin, bendroflumethiazide, benzapril, benzclortriazide, benzthiazide, BIBR-277, butizide, candesartan, captopril, ceranopril, chlorothalidone, chlorothiazide, cilazapril, cilexetil, clonidine, cromakalim, cryptenamine acetates and cryptenamine tannates, CSG 22492C, cyclopenthiazide, cyclothiazide, delapril, deserpidine, diazoxide, digitalis, digoxin, diflusinal, diltiazem, dopamine, dobutamine, doxazosin, enalapril, enalaprilat, eprosartan, ethacrynic acid, ethiazide, felodipine, FK 744, FK 906, fosinopril, furosemide, guanabenz, guanethidine, guanethidine sulfate, hydralazine hydrochloride, hydrochlorothiazide, hydroflumethiazide, idrapril, imidapril, irbesartan, isradipine, ketanserin, libenzapril, lisinopril, losartan, merethoxylline procaine, methylchlothiazide, metolazone, metoprolol, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, milrinone, minoxidil, moexipril, moveltopril, nadolol, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, nitroglycerine, nitroprusside, pargyline hydrochloride, penflutazide, pentopril, perindopril, pinacidil, pindolol, polythiazide, prazosin, prentyl, propranolol, quinapril, quinapril hydrochloride, quinethazone, ramapril, rauwolfia serpentina, rescinnamine, reserpine, SK&F-108566, sodium ethacrynate, sodium nitroprusside, spirapril, spironolactone, SR-47436, synecor, tasosartan, TCV-116, telmisartan, temocapril, teprotide, terazosin, ticrynafan, timolol maleate, triamterene, trichlormethazide, trandolopril, trichlormethiazide, trimethophan camsylate, UK-73900, utibapril, valsartan, verapamil, zabicipril, zalicipril, zofenopril, zofenopril calcium, zolasartan, and admixtures and combinations thereof.

10. The method of Claim 9 wherein the growth hormone secretagogue is selected from the group consisting of:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, $OC(O)$, $C(O)O$, or $-CR_2=CR_2-$, or -C≡C-,

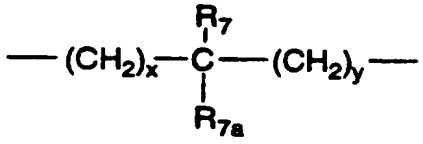
and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)_2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};
R_{2a} is hydrogen, or C_1-C_6 alkyl;

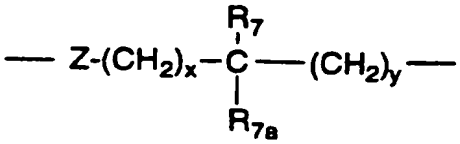
R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;
R_6 is hydrogen or C_1-C_6 alkyl;

A is:



or



wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, -$(CH_2)_q$-aryl, -$(CH_2)_q$-$C(O)OR_2$, -$(CH_2)_q$-$C(O)O(CH_2)_q$-aryl, or -$(CH_2)_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R_9 is selected from the group consisting of:
-R_2, -$(CH_2)_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,

and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 $-OR_{2a}$, $-O(CH_2)_q$ aryl, 1 to 2 $-C(O)OR_{2a}$, 1 to 2 $-C(O)O(CH_2)_q$ aryl, 1 to 2 $-C(O)N(R_{2a})(R_{2a})$, 1 to 2 $-C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R_{2a}$, $-S(O)_mR_{2a}$, $-C(O)NHSO_2(CH_2)q$-aryl, $-SO_2NHC{\equiv}N$, $-SO_2NHC(O)R_{2a}$, $-SO_2NHC(O)(CH_2)_q$aryl, $-N(R_2)C(O)N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)N(R_{2a})(CH_2)_q$-aryl, $-N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)R_{2a}$, $-N(R_{2a})C(O)(CH_2)q$ aryl, $-OC(O)N(R_{2a})(R_{2a})$, $-OC(O)N(R_{2a})(CH_2)_q$ aryl, $-SO_2(CH_2)_qCONH$-$(CH_2)w$NHC(O)R_{11}, wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1, or 2;

q may optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring; and pharmaceutically acceptable salts and individual diastereomers thereof.

11. The method of Claim 9 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

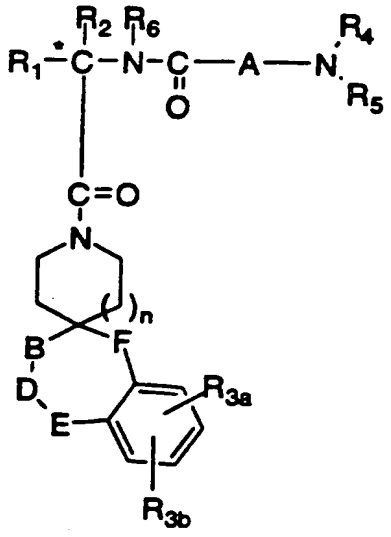
12. A method of diminishing loss of body weight in a mammal following congestive heart failure which comprises the administration of a therapeutically effective amount of a growth hormone secretagogue.

13. The method of Claim 12 wherein the growth hormone secretagogue is an orally active growth hormone secretagogue.

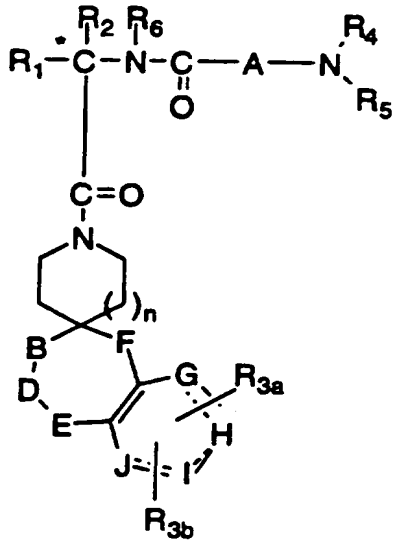
14. The method of Claim 13 wherein the growth hormone secretagogue is orally administered.

15. The method of Claim 12 wherein the mammal is a human.

16. The method of Claim 12 wherein the growth hormone secretagogue is selected from the group consisting of:



Formula I



Formula II

wherein:

R1 is selected from the group consisting of:

-C1-C10 alkyl, -aryl, -aryl-(C1-C6 alkyl),

-C3-C7 cycloalkyl-(C1-C6alkyl), -C1-C5alkyl-K-C1-C5 alkyl, -aryl(C0-C5alkyl)-K-(C1-C5 alkyl),

-C3-C7 cycloalkyl(C0-C5 alkyl)-K-(C1-C5 alkyl),

wherein K is O, S(O)m, N(R2)C(O), C(O)N(R2), OC(O), C(O)O, or -CR2=CR2-, or -C≡C-,

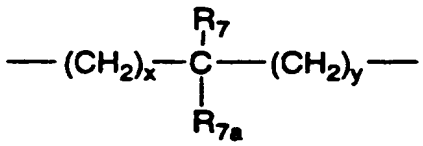
and wherein the aryl groups are as defined below and the R2 and alkyl groups may be futher substituted by 1 to 9 halogen, S(O)mR2a, 1 to 3 OR2a, or C(O)OR2a, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C1-C6 alkyl, 1 to 3 halogen, 1 to 2 -OR2, methylenedioxy, -S(O)mR2, 1 to 2 -CF3, -OCF3, nitro, -N(R2)(R2), -N(R2)C(O)R2, -C(O)OR2, -C(O)N(R2)(R2), -SO2N(R2)(R2), -N(R2)S(O)2 aryl, and -N(R2)SO2R2;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};
R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m$(C_1-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;
R_6 is hydrogen or C_1-C_6 alkyl;

A is:



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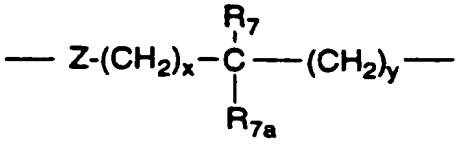


wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -N=CR_{10}- or -CR_{10}=N-, or B and D, or D and E taken together may be -CR_8=CR_{10}-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, -$(CH_2)_q$-aryl, -$(CH_2)_q$-$C(O)OR_2$, -$(CH_2)_q$-$C(O)O(CH_2)_q$-aryl, or -$(CH_2)_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R_9 is selected from the group consisting of:
-R_2, -$(CH_2)_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,

and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 $-OR_{2a}$, $-O(CH_2)_q$ aryl, 1 to 2 $-C(O)OR_{2a}$, 1 to 2 $-C(O)O(CH_2)_q$ aryl, 1 to 2 $-C(O)N(R_{2a})(R_{2a})$, 1 to 2 $-C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R_{2a}$, $-S(O)_mR_{2a}$, $-C(O)NHSO_2(CH_2)q$-aryl, $-SO_2NHC{\equiv}N$, $-SO_2NHC(O)R_{2a}$, $-SO_2NHC(O)(CH_2)_q$aryl, $-N(R_2)C(O)N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)N(R_{2a})(CH_2)_q$-aryl, $-N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)R_{2a}$, $-N(R_{2a})C(O)(CH_2)q$ aryl, $-OC(O)N(R_{2a})(R_{2a})$, $-OC(O)N(R_{2a})(CH_2)q$ aryl, $-SO_2(CH_2)_qCONH$-$(CH_2)w$NHC(O)R_{11}, wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1, or 2;

q may optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring; and pharmaceutically acceptable salts and individual diastereomers thereof.

17. The method of Claim 12 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

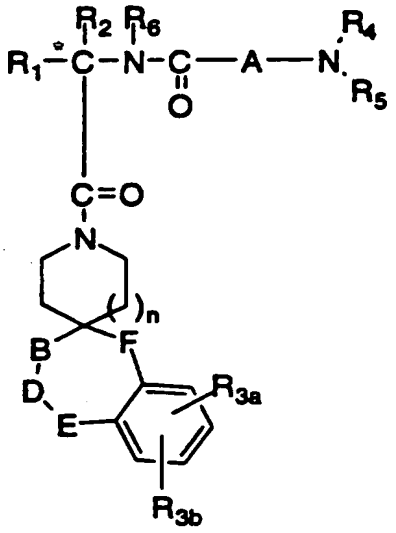
18. A method of enhancing recovery of a mammal following congestive heart failure which comprises the administration of a therapeutically effective amount of a growth hormone secretagogue.

19. The method of Claim 18 wherein the growth hormone secretagogue is an orally active growth hormone secretagogue.

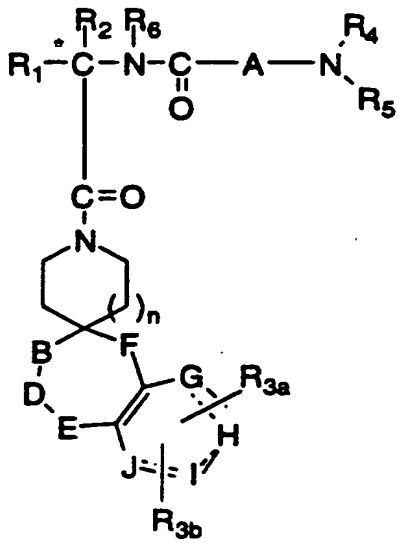
20. The method of Claim 19 wherein the growth hormone secretagogue is orally administered.

21. The method of Claim 18 wherein the mammal is a human.

22. The method of Claim 18 wherein the growth hormone secretagogue is selected from the group consisting of:



Formula I



Formula II

wherein:

R_1 is selected from the group consisting of:

-C_1-C_{10} alkyl, -aryl, -aryl-(C_1-C_6 alkyl),

-C_3-C_7 cycloalkyl-(C_1-C_6alkyl), -C_1-C_5alkyl-K-C_1-C_5 alkyl, -aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl),

-C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl),

wherein K is O, $S(O)_m$, $N(R_2)C(O)$, $C(O)N(R_2)$, $OC(O)$, $C(O)O$, or $-CR_2=CR_2-$, or -C≡C-,

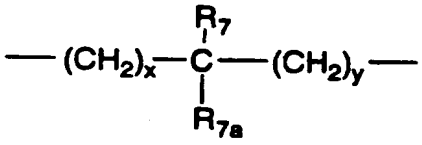
and wherein the aryl groups are as defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, $S(O)mR_{2a}$, 1 to 3 OR_{2a}, or $C(O)OR_{2a}$, and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 $-OR_2$, methylenedioxy, $-S(O)_mR_2$, 1 to 2 $-CF_3$, $-OCF_3$, nitro, $-N(R_2)(R_2)$, $-N(R_2)C(O)R_2$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, $-SO_2N(R_2)(R_2)$, $-N(R_2)S(O)2$ aryl, and $-N(R_2)SO_2R_2$;

R_2 is selected from the group consisting of:
hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};
R_{2a} is hydrogen, or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of: hydrogen, halogen, -C_1-C_6 alkyl, -OR_2, cyano, -OCF_3, methylenedioxy, nitro, -$S(O)_mR$, -CF_3 or -$C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, substituted C_1-C_6 alkyl wherein the substituents are selected from 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, -$S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form -$(CH_2)_rL_a(CH_2)_s$- where L_a is -$C(R_2)_2$-, -O-, -$S(O)_m$-, or -$N(R_2)$-, where r and s are independently 1 to 3 and R_2 is as defined above;
R_6 is hydrogen or C_1-C_6 alkyl;

A is:



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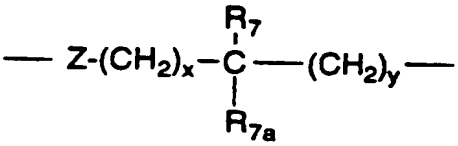

wherein x and y are independently 0-3;
Z is N-R_2 or O;

R_7 and R_{7a} are independently selected from the group consisting of: hydrogen, -C_1-C_6 alkyl, -OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are selected from imidazolyl, phenyl, indolyl, p-hydroxyphenyl, -OR_2, 1 to 3 fluoro, -$S(O)_mR_2$, -$C(O)OR_2$, -C_3-C_7 cycloalkyl, -$N(R_2)(R_2)$, -$C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently selected from the group consisting of: -$C(R_8)(R_{10})$-, -O-, C=O, -$S(O)_m$-, or -NR_9-, such that one or two of B, D, E, or F may be optionally absent to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be -$C(R_8)(R_{10})$- or C=O only when one of the remaining B, D, E and F groups is simultaneously -O-, -$S(O)_m$-, or -NR_9-, or
B and D, or D and E taken together may be -$N{=}CR_{10}$- or -$CR_{10}{=}N$-, or B and D, or D and E taken together may be -$CR_8{=}CR_{10}$-, provided one of the other of B and E or F is simultaneously -O-, -$S(O)_m$-, or -NR_9-;

R_8 and R_{10} are independently selected from the group consisting of: hydrogen, -R_2, -OR_2, -$(CH_2)_q$-aryl, -$(CH_2)_q$-$C(O)OR_2$, -$(CH_2)_q$-$C(O)O(CH_2)_q$-aryl, or -$(CH_2)_q$-(1H-tetrazol-5-yl), where the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 -OR_2 or 1 to 2 -$C(O)OR_2$;

R_9 is selected from the group consisting of:
-R_2, -$(CH_2)_q$-aryl, -$C(O)R_2$, -$C(O)(CH_2)_q$-aryl, -SO_2R_2, -$SO_2(CH_2)_q$-aryl, -$C(O)N(R_2)(R_2)$, -$C(O)N(R_2)(CH_2)_q$-aryl, -$C(O)OR_2$, 1-H-tetrazol-5-yl, -SO_3H, -$SO_2NHC{\equiv}N$, -$SO_2N(R_2)$aryl, -$SO_2N(R_2)(R_2)$,

and wherein the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 $-OR_{2a}$, $-O(CH_2)_q$ aryl, 1 to 2 $-C(O)OR_{2a}$, 1 to 2 $-C(O)O(CH_2)_q$ aryl, 1 to 2 $-C(O)N(R_{2a})(R_{2a})$, 1 to 2 $-C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R_{2a}$, $-S(O)_mR_{2a}$, $-C(O)NHSO_2(CH_2)q$-aryl, $-SO_2NHC{\equiv}N$, $-SO_2NHC(O)R_{2a}$, $-SO_2NHC(O)(CH_2)_q$aryl, $-N(R_2)C(O)N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)N(R_{2a})(CH_2)_q$-aryl, $-N(R_{2a})(R_{2a})$, $-N(R_{2a})C(O)R_{2a}$, $-N(R_{2a})C(O)(CH_2)q$ aryl, $-OC(O)N(R_{2a})(R_{2a})$, $-OC(O)N(R_{2a})(CH_2)_q$ aryl, $-SO_2(CH_2)_qCONH$-(CH_2)wNHC(O)R_{11}, wherein w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1, or 2;

q may optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that at least one is a heteroatom and one of G, H, I or J may be optionally missing to afford a 5 or 6 membered heterocyclic aromatic ring; and pharmaceutically acceptable salts and individual diastereomers thereof.

23. The method of Claim 18 wherein the growth hormone secretagogue is selected from the group consisting of:

1) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

2) N-[1(R)-[(1,2-Dihydro-1-methanecarbonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

3) N-[1(R)-[(1,2-Dihydro-1-benzenesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

4) N-[1(R)-[(3,4-Dihydro-spiro[2H-1-benzopyran-2,4'-piperidin]-1'-yl) carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

5) N-[1(R)-[(2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinolin-4,4'-piperidin]-1'-yl)carbonyl]-2-(indol-3-yl)ethyl]-2-amino-2-methyl-propanamide;

6) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

7) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide mesylate salt;

8) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(2',6'-difluorophenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

9) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

10) N-[1(S)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl) carbonyl]-2-(phenylmethylthio)ethyl]-2-amino-2-methylpropanamide;

11) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-phenylpropyl]-2-amino-2-methyl-propanamide;

12) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-3-cyclohexylpropyl]-2-amino-2-methyl-propanamide;

13) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-4-phenylbutyl]-2-amino-2-methyl-propanamide;

14) N-[1(R)-[(1,2-Dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

15) N-[1(R)-[(1,2-Dihydro-1-methanesulfonyl-5-fluorospiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(5-fluoro-1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

16) N-[1(R)-[(1,2-Dihydro-1-(2-ethoxycarbonyl)methylsulfonylspiro-[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(1H-indol-3-yl)ethyl]-2-amino-2-methylpropanamide;

17) N-[1(R)-[(1,2-Dihydro-1,1-dioxospiro[3H-benzothiophene-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide;

and pharmaceutically acceptable salts thereof.

The Patent Office

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Application No: GB 9622440.7
Claims searched: None

Examiner: Dr Carol Davies
Date of search: 7 April 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O):

Int Cl (Ed.6): A61K

Other: ONLINE: WPI; CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	None	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.